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SO-CALLED "ATYPICAL PNEUMONIA" AMONG COLLEGE STUDENTS*

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THERE has recently been noted among the students at Harvard University a marked increase in the incidence of an acute infection the etiology of which is little understood. Reimann[1, 2] in 1939 called attention to isolated cases of a form of pneumonia in adults, apparently not caused by bacteria or by the virus of epidemic influenza. From 2 of the cases that he reported during the years 1938-1939 a filterable infectious agent was recovered. Smiley, Showacre, Lee and Ferris[3] in the same year reported what they called "acute interstitial pneumonitis" in the student body of Cornell University. Murray[4] reported a group of so-called "atypical pneumonias" occurring in Harvard students during the winter of 1936-1937. Within the past year, Finland and Dingle[5, 6] discussed in great detail the various types of pneumonias and included in their discussion all the known pneumonias not caused by a definite bacterial infection. They reviewed the literature thoroughly for the types of pneumonia which had been more frequent in recent years and in which the pulmonary lesions were not due to the common pathogenic bacteria. They called attention to the fact that atypical pneumonia was almost entirely limited to adolescents and young adults. They also believed that little is known about the mode and manner of spread of this illness. The general consensus, they said, is that it is transmitted by contact but is not highly communicable. Although the disease is commonly referred to as "virus pneumonia," no one of these authors was able to prove or disprove that these somewhat related pulmonary diseases are due to a virus. They were all in agreement, however, that it is not of bacterial origin.

Since July, 1942, there have been admitted to the Stillman Infirmary some 75 cases of atypical pneumonia, proved by clinical and roentgenologic evidence. No case was considered so proved unless the symptoms were fairly typical and x-ray examination of the chest showed changes compatible with atypical pneumonia. This a great increase over any number admitted in recent years. During the academic year of 1938-1939, of 2128 admissions there were 81 cases diagnosed as bronchopneumonia. During 1939-1940, of the total of 1943 patients admitted only 15 were diagnosed as having bronchopneumonia. During 1940-1941, during which time there were 2104 admissions, only 7 cases were diagnosed as bronchopneumonia. In 1941-1942, there were 15 diagnoses of atypical pneumonia among 1595 admissions. From July 1 to December 20, 1942, there were 75 cases of atypical pneumonia among some 884 admissions. This is 8 per cent of the total admissions in this period, a startling percentage indicating the high incidence of this illness at the present time.

The average age of patients in this series, all of whom were males, was twenty, the youngest patient being seventeen and the oldest twenty-four. This does not mean that the illness is confined entirely to this age group; it may occur in older persons, although perhaps with less frequency.

INFECTIOUSNESS

The question of infectiousness of this disease is most debatable at the present time. It is the belief of some[1, 2] that it is highly contagious, but from a practical viewpoint, considering our experience during the last few months, it is surprising that none of the personnel of the institution caring for these patients have been ill although no extraordinary precautions were taken. Moreover, there was no case in which both of two roommates were afflicted with the disease. In one case, a boy who had been exposed to atypical pneumonia patients in an open ward was readmitted two

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weeks later with the disease. For the most part these patients were kept in the same ward as were students with ordinary respiratory infections and a mixture of other unrelated illnesses. With this experience, it is most difficult to interpret accurately the infectiousness of the disease, and it has not seemed worth while to use infectious precautions such as are required for the handling of a highly contagious illness. It may well be that, as suggested by Bock[7] and Reimann,[2] this infection is a manifestation in one patient of atypical pneumonia, whereas in another it manifests itself in a no more serious way than a "cold." On this assumption, it does not appear to be necessary to use extraordinary precautions in handling cases of atypical pneumonia when the free movement of those suffering from "colds" is permitted. The major precaution is, perhaps, the simple requirement that none of the staff shall appear on duty while afflicted with an acute respiratory infection, regardless of its severity.

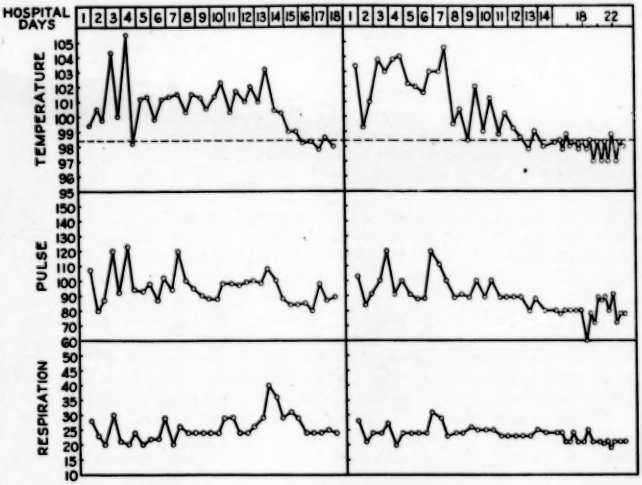

FIGURE 1. *Charts of Case 1 (left) and Case 2 (right).*

SYMPTOMS

The symptoms were extremely variable but the absence in most cases of any symptoms referable to the respiratory system was noticeable. The predominating symptoms at the time of admission were easy fatigue, general malaise, muscle pains, headache, an alternate feeling of chilliness and feverishness and, rarely, extreme lethargy. In a few cases cough, although of a minor character, was present, and in some a history of a head cold of several days' duration was obtained. The onset of the disease was insidious, chest pain was absent in all cases, and cough in the great majority of cases was absent or minor with the exception of several cases to be discussed later. In no case was there expectoration of sputum of any noteworthy amount, or of prune-juice or bloody sputum.

PHYSICAL EXAMINATION AND HOSPITAL COURSE

The physical examination at the time of admission showed an average temperature of 102°F., the lowest being 100 and the highest 104. The remainder of the examination was negative unless the student had had the illness for five to six days before admission, in which case coarse rales could be heard in some area of the lung field. The white-cell count was within the normal range with one or two exceptions, when it was 14,000 or 15,000 on the first day but was below 10,000 on the second. The initial elevation in these exceptions may have been due to dehydration. A noticeable leukopenia was absent in the great majority of cases, the lowest count being 5200 and the average 6800. The differential count and the blood smear were characteristically in the normal range. The only possible way of making a diag-

nosis in the early stages is by means of x-ray examination of the chest. In some cases the findings were normal during the first few days of the illness (Case 1) and for three or four days after admission, although the symptoms of general

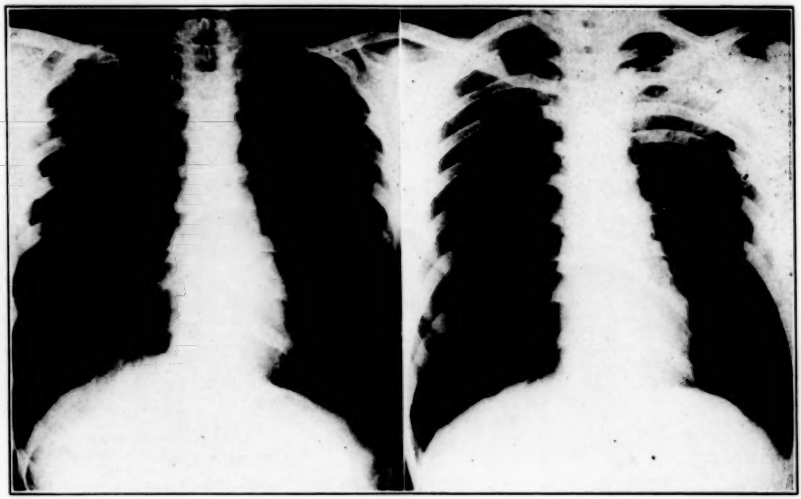

FIGURE 2. *Case 1.*

The film on the left was taken on the second hospital day. There is linear increased density in the left upper lobe; otherwise the chest appears normal. The one on the right, taken on the fourth hospital day, shows an area of diffuse haziness occupying the left infraclavicular region that is consistent with pneumonia.

malaise, chilliness and so forth were marked and the temperature was high.

There seemed to be no predominance as to the area involved, although generally speaking the bases of the lungs were more frequently involved than were the upper and middle lobes. The amount of consolidation shown by x-ray examination was extremely variable. In some cases, the roentgenologic examination showed only a small area of consolidation without further progression, but in others the x-ray film was most startling in its appearance — in fact, so much so that it closely resembled the picture of miliary tuberculosis (Cases 2 and 3). The x-ray appearance was in most cases that of patchy consolidation throughout the part of the lung involved, but in approximately 20 per cent of the cases it showed frank consolidation of one lobe or another (Case 4).

In all cases except those showing lobar consolidation by roentgen ray, bronchial breathing or other signs of consolidation were absent, and the usual first physical sign was the appearance of coarse rales, most often on the fifth or sixth day, but sometimes as late as the tenth. Frequently at the time of the appearance of the rales the patient was feeling better and the temperature was on the down grade. Dyspnea was not present in the great majority of cases, and the respiratory rate in all except a few cases was not increased beyond the point that one would expect in a patient with fever. In some cases a rapid respiratory rate was noted (Case 3), but in these patients it was due to a shallow, panting respiration rather than to true dyspnea. The shallow, rapid respiration was due largely to the fact that deep breathing or even normal chest excursion precipitated paroxysms of coughing. Cyanosis was present in only 2 cases, and then to only a moderate degree.

The average period of hospitalization was ten days, the shortest being six days and the longest thirty days. The short hospitalization of some patients does not mean that the disease was completely over in this time. Most of the patients had been ill for four or five days before admission, and in other cases they were discharged home for convalescence before they could be considered ambulatory.

In all cases the sputum showed no typable pneumococci, and in a fair number repeated sputum examination for acid-fast bacilli was negative. Surprisingly little sputum was expectorated, regardless of how much involvement by clinical or x-ray examination was noted. Cough, which was a minor symptom in most cases, was severely annoying in several (Cases 2 and 3). Here it was dry and paroxysmal, and somewhat resembled whooping cough without the whoop.

In rare cases extreme lethargy was a noticeable symptom. The cause of this was clinically difficult to determine, since the patients showed no more fever, changes in the chest as revealed by x-ray study, or headache than did the average patient with the disease. Likewise, there was no stiffness of the neck or neurologic changes on physical examination. In 1 case, a severe conjunctivitis and stomatitis developed. The conjunctivitis was not purulent, — stained smears and cultures were negative, — but the conjunctivas were edematous, swollen and markedly reddened. The appearance of the mouth was also most unusual, somewhat resembling that found in fungus stomatitis but not typical of that condition. The conjunctivitis and stomatitis both cleared without specific therapy in ten days.

The complications were nil. There were no cases of empyema or otitis media, and no development of other respiratory conditions. Moreover, so far as known there have been no recurrences or relapses.

Treatment

There is no specific therapy for this disease. The sulfonamide drugs have been tried on occasion, but have been of no benefit. Bed rest and fluids are essential. Excess salt is of value if perspiration is excessive. Cough, which is of a severe nature in a few cases, should be controlled by opiates if necessary. The absence of dyspnea, cyanosis and a normal respiratory rate does not contraindicate the use of opiates as in the ordinary pneumococcal pneumonia.

The appetite in the great majority of these cases was poor during the illness, and it may be of value to supplement the diet with a high vitamin B intake in an effort to stimulate caloric intake.

Although the average hospital stay was only ten days, the average time of disability was twenty-one days. Practically all these patients lost ten to twenty pounds during their illness, became easily fatigued after getting out of bed, and were unable to resume their normal activities for ten or twelve days after discharge.

Four cases that were somewhat unusual in their manifestations are as follows:

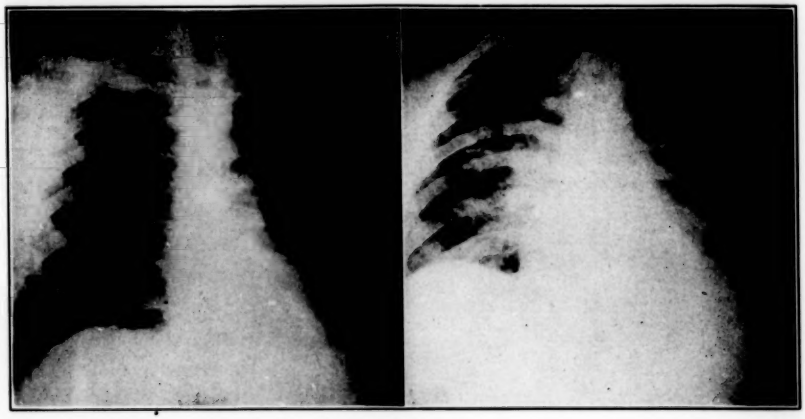

Figure 3. *Case 2.*

The film on the left, taken on the second hospital day, shows slight density lateral to the apex of the heart that is consistent with consolidation in the left lower lobe. That on the right, taken on the eighth hospital day, shows marked density in the medial portions of both lower lobes.

Case Reports

Case 1. H. H. was admitted October 16, 1942, with the chief complaint of slight chills and fever, general malaise and slight cough for the previous 2 days. The admission temperature was 99.4°F. (Fig. 1). Physical examination was negative. On the following day, an x-ray film of the chest (Fig. 2) showed increased density in the left upper lobe. On the 3rd hospital day the temperature was 104.6°F., and on the 4th, 106°F., following a chill. Physical examination was normal throughout this period; the amount of sputum was small, and no pneumococci or tubercle bacilli were found. On the 4th day an x-ray film showed an area of diffuse haziness in the left infraclavicular area. The only abnormal physical findings appeared on the 11th day, when coarse, crackling rales were heard throughout the lower and middle left lung field, especially anteriorly and in the axillary line. The patient was discharged home for convalescence on the 18th day, with rales still present in the left lung, although the temperature had been normal for 2 days.

Case 2. S. O. was admitted on September 4, 1942. Illness began with alternate chilly and feverish sensations, accompanied by general malaise, fever and a slight, dry, nonproductive cough. The temperature on admission was 104°F. (Fig. 1). Physical examination was negative with the exception of evidence of fever. The white-cell count was 14,800. The sputum on several examinations showed no pneumococci; likewise several tests for tubercle bacilli were negative. An x-ray film (Fig. 3) taken on the 2nd hospital day showed slight density lateral to the apex of the heart. The report on a film taken on the 13th day was as follows: "There is fine mottling throughout both lung fields; the fine miliary processes are very suggestive of miliary tuberculosis." On the 22nd day there was still a small amount of density lateral to the apex of the heart, but otherwise the lung fields were clear. The most annoying symptom in this patient was a cough that was paroxysmal, dry and nonproductive; it was so annoying that Dilaudid was given every 3 hours for relief. Because of an original white-cell count of 14,800, the patient was started on sulfadiazine in large doses, which was maintained for 4 days without benefit.

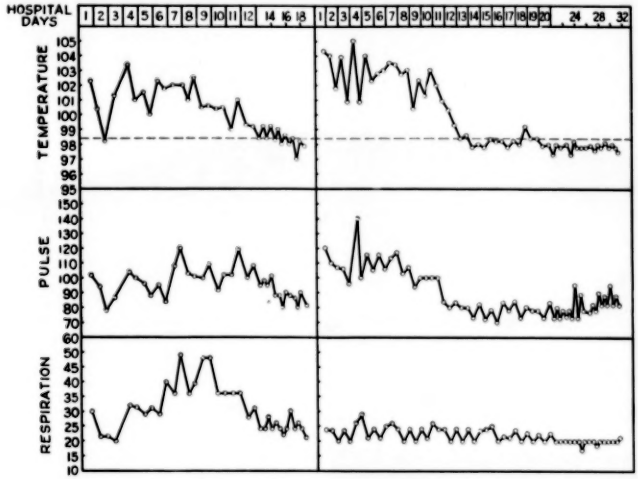

Figure 4. *Charts of Case 3 (left) and Case 4 (right).*

Case 3. D. G. was admitted on October 8, 1942, with a history of not having felt well for 3 days; the symptoms consisted of nasal congestion, slight cough, general malaise and a feeling of feverishness. The temperature on admission was 102.5°F. (Fig. 4). Physical examination was negative except for a warm, moist skin. The white-cell count was 6700, with a normal differential. On the 2nd day, an x-ray film (Fig. 5) showed haziness in the left lower lobe. Physical examination of the chest remained negative until the 7th day, when coarse rales were heard at both bases posteriorly. Two days later rales were heard throughout the entire left lung field, and an x-ray film the following day showed a miliary process involving the entire left lung and the upper portion of the right lung. The physical signs quickly abated and were absent at the time of discharge. Several sputum examinations revealed no pneumococci or tubercle bacilli. The cough was the most annoying symptom, and it was necessary to give Dilaudid every 3 hours for many days. Several subsequent white-cell counts were normal and the patient was discharged on the 19th day to convalesce at home.

Case 4. M. K. was admitted on January 15, 1941.* He had not felt well for 2 days before admission, the

*This case, although the illness occurred in a previous year, was included because of its interesting manifestations.

symptoms being general malaise, pains in the muscles, slight chills and fever, and a mild cough. On admission, the temperature was 104°F. (Fig. 4), and physical examination was negative; the white-cell count was 16,700, with a normal differential. A count the following day was 8000, with 90 per cent neutrophils. The patient was started on large doses of sulfathiazole 2 days after admission. This medication was continued for 3 days without benefit. The first clinical signs in the chest were heard on the 6th hospital day, when signs of frank consolidation were observed at the right base. On the following day, an x-ray film (Fig. 6) revealed complete consolidation of the right middle lobe and of a large portion of the right lower lobe. The patient continued to run a rather high temperature, which gradually subsided by lysis on the 13th hospital day. On the 18th day, moist rales at both bases were still present. The lung signs gradually abated, and the chest became clear one week before discharge. This case is most interesting in that the white-cell count continued to rise. It reached a high of 22,800 on the 13th day, when the temperature was normal. Furthermore, an eosinophilia developed, which went as high as 26 per cent. The count did not return to normal until the 32nd day, 1 week after all the chest signs had disappeared, and 19 days after the temperature had returned to normal. The cause of this queer blood picture could not be explained.

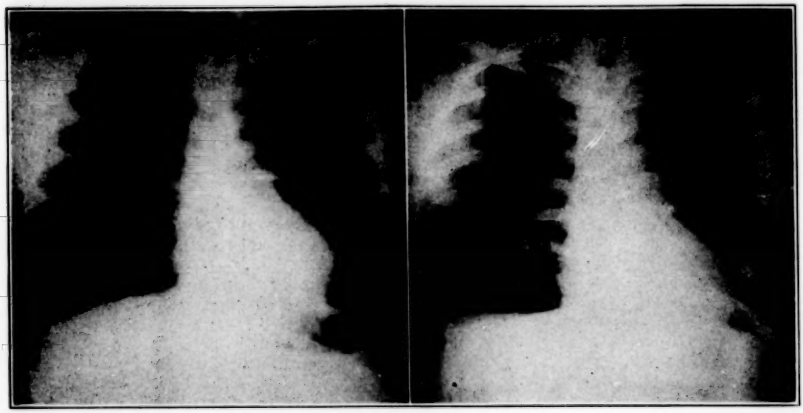

FIGURE 5. *Case 3.*

The film on the left, taken on the second hospital day, shows haziness in the left lower lobe lateral to the heart. That on the right, taken on the tenth day, shows a miliary process involving the entire left lung, which is most marked at the base; there is also a miliary process in the upper portion of the right lung, probably in the upper lobe.

FIGURE 6. *Case 4.*

This film, taken on the seventh hospital day, shows complete consolidation of the right middle lobe and of a large portion of the right lower lobe.

SUMMARY

A clinical study of so-called "atypical pneumonia" among 75 college students is reported. The patients were males and ranged from seventeen to twenty-four years of age, with an average age of twenty years. The average period of hospitalization was ten days, but the disability period averaged twenty-one days.

There were no serious complications and all the patients recovered without incident. Four cases, which were somewhat unusual in character, are discussed in detail, with clinical charts and roentgenologic data.

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INHALATIONAL THERAPY IN THE TREATMENT OF SERIOUS RESPIRATORY DISEASE*

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THE use of oxygen for the treatment of various types of anoxemia has increased tremendously. One generally appreciates that every physiologic function is only as efficient as its supply of oxygen. Reviews of the physiologic principles on which oxygen therapy is based have been made by Haldane,[1] Haldane and Priestly,[2] Lundsgaard and Van Slyke,[3] Peters and Van Slyke,[4] Barcroft,[5] Meakins and Davies[6] and others. Reviews of its practical application have been made by Boothby and his associates,[7-9] Barach and his associates[10-12] and others.

The use of mixtures of helium and oxygen for the treatment of the various anoxemias associated with respiratory and cardiac disease has increased largely through the investigative efforts of Barach. He[13] has repeatedly demonstrated improvement in vital capacity, marked reduction in pulmonary ventilation, diminished tidal volume, diminished residual air and increased expiratory and inspiratory velocity rates with properly directed inhalational therapy in patients with asthma and emphysema. Barach and his associates have stressed the value of oxygen and helium and oxygen mixtures with and without positive pressure in a large series of papers based on experimental and clinical observations. The use of these mixtures under positive pressure has not become so widespread as it should have. Most clinicians are discouraged by the technical details and apparatus necessary for this type of inhalational therapy. However, its value as an adjunct in the management of the desperately ill patient with respiratory disease should overcome this attitude.

Equipment for Inhalational Therapy

The following are the more commonly used methods of administering oxygen: the nasal or nasopharyngeal catheter, oxygen face masks and tents and the various types of enclosing tents. Each method has its special advantages and disadvantages. With the above methods oxygen can be given in concentrations of 40 to 75 per cent. With the new B. L. B. inhalation mask and oxygen flows of 5 to 12 liters per minute, very high concentrations of oxygen can be administered quite economically.

Eckman and Barach[14] have described in detail the various types of apparatus that they found useful. The helium-oxygen pressure apparatus is a most effective one for giving oxygen or helium and oxygen mixtures with or without positive pressure. The percentage concentrations of the mixtures can be exactly controlled. Positive pressures up to 6 cm. of water can be applied to the inner surface of the lung during both inspiration and expiration. The apparatus consists of a gas-tight motor blower, two canisters for the carbon dioxide absorber, a rheostat to determine the volume of air flow and its temperature, tubal connections, an ice-containing cabinet and a plastocele hood in which the patient's head lies, with closure made by a soft-rubber band collar. In this rebreathing circuit only the oxygen is used up.

In a recent paper Barach and Molomut[15] describe a modification of the Barach-Eckman[16] mask. This new type of injector mask is metered for positive pressures up to 4 cm. of water in the expiratory phase only. Along with the injector (oxyator principle) it may be used to deliver 40 to 95 per cent oxygen or helium and oxygen mixtures with or without positive pressure during expiration. It can be used to supplement the above-described hood apparatus. The mask is a credit to the ingenuity of the authors. Both the hood and the mask apparatus were employed in the present series.

Use of Helium

Helium is an inert, colorless, odorless, noncombustible gas of low molecular weight.[4] It has a specific gravity one seventh of that of nitrogen and one eighth of that of oxygen. It has a low

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coefficient of solubility, being 40 per cent less soluble in water than is nitrogen. It is nearly three times more diffusible than nitrogen. Hence very little helium is dissolved or lost in the body. In comparison, nitrogen under pressure is much more soluble in body fluids and furthermore has an affinity for lipids.

In 1934 Barach[17] proved the biologic inertness of helium. A mixture of 80 per cent helium and 20 per cent oxygen is one third as heavy as air. Its lightness suggested to Barach that it could be moved to and from the lungs in obstructive dyspneas more easily than air. Furthermore, a lighter-than-air mixture will go through a constricted orifice more easily. The pressure required for the movement of an 80 per cent helium and 20 per cent oxygen mixture would be about half that required for air through a similarly constricted orifice. It should be possible with helium and oxygen mixtures to compensate for approximately a 50 per cent constriction in the lumen of the tubal respiratory tract. The more localized the obstruction, the better the effect. This saving in respiratory effort may be of life-saving value.

The chief use of helium-oxygen mixtures is in the treatment of obstructive dyspnea from the larynx to the bronchiole (Barach[17, 18] and Eversole[19]). It should always be given a trial in any type of respiratory obstruction in an effort to avoid tracheotomy, with its inherent complications. Helium when mixed with oxygen decreases the effort required for pulmonary ventilation, and lowering of the negative intrapleural pressure follows. Addition of positive pressure further accentuates this lowering.

The proper percentage of oxygen in the helium-oxygen mixture depends on the degree of anoxemia. The proper percentage of helium depends largely on the degree of mechanical obstruction interfering with the inflation of the alveoli. By using separate tanks, one containing 80 per cent helium and 20 per cent oxygen and the other 100 per cent oxygen, connected by a Y tube to either the hood or the mask apparatus, the desired percentage of the mixture can be changed at will to suit the patient's physiologic needs. At least 20 per cent oxygen must be administered. It is doubtful whether helium will be valuable if the mixture contains more than 33 to 35 per cent oxygen. Continuous residence in the hood may be maintained without much discomfort for many days. In one of Barach's reported cases the patient required helium-oxygen therapy under positive pressure for six days. The metered mask may be kept on for one to three days, and perhaps longer with proper rest periods. The problem of length of residence in hood or mask varies with the degree of anoxemia, dyspnea and respiratory fatigue and the presence of psychic factors. The higher percentages of oxygen should not be used continuously, for pulmonary irritation has been described. The change from hood to mask or oxygen tent should be gradual with a progressive reduction in the percentage of oxygen, or intermittent treatment should be carried out before complete cessation.

Treatment Of Pulmonary Edema With Positive Pressure

Pulmonary edema occurs frequently in a wide range of respiratory and circulatory diseases and usually constitutes an acute medical emergency. It has been found clinically that positive-pressure inhalation of oxygen or helium and oxygen clears up the signs of pulmonary edema promptly. Barach[20] in his most recent paper once again demonstrated the value of properly directed positive-pressure inhalational therapy in 5 patients critically ill with pneumonia. He states that positive pressure is like putting a finger on the capillaries and stopping their oozing.

Barach[21–23] has summarized the sequence of events that follow resistance or obstruction to inspiration. There is at first a rapid and progressive increase in the intrapleural negative pressure in order to force sufficient air into the lung. Other changes, characterized by pulmonary edema and final respiratory failure, may follow. Barach and his associates[24, 25] have repeatedly demonstrated that when oxygen or helium-and-oxygen mixtures are taken under positive pressures, the abnormally elevated negative intrapleural pressure is diminished and dyspnea is alleviated. Nature provides a helpful internal mechanism, as observed by Barach, in the severe asthmatic patient pursing his lips in expiration, and in the pneumonic patient grunting and groaning with expirations. The expiratory grunt maintains a more patent airway and helps to prevent pulmonary edema.

Properly controlled positive pressure is extremely useful in the management of pulmonary edema. The moist, bubbling rales have been seen to clear up within fifteen to forty-five minutes in a series of patients with underlying bronchial asthma, pneumonia, left-ventricular failure, mediastinal obstruction and gas poisoning. The signs of pulmonary edema usually remain absent as long as the pressure is applied or until the original cause has been removed. The application of a gentle internal distending force serves to keep the bronchioles patent and opposes the hydrostatic pressure within the capillaries.

Generally, positive pressures of 2 to 6 cm. of water are sufficient for preventing or treating

pulmonary edema. Pressures above 6 cm. may diminish the return flow of blood to the right side of the heart. Theoretically, shock may be considered a contraindication to the use of positive pressure.

Inhalation of Vaporized Bronchodilator Solutions

The value of oral inhalations of vaporized sprays of various bronchodilator solutions with the use of a hand-bulb atomizer was established on a sound basis by Graeser and Rowe.[26] Richards, Barach and Cromwell[27] described the technic of continuous vaporization of bronchodilator solutions for the treatment of bronchial asthma, emphysema, acute bronchiolitis and various so-called "virus pneumonias." They used 1 or 2 cc. of 1:100 epinephrine and 1 per cent Neo-Synephrine, alone or in combination. The solution was placed in the vaporizer and oxygen was passed through it from the pressure tank at the rate of 4 to 7 liters per minute. The patient simply held the nozzle of the vaporizer in his mouth and breathed quietly. This therapy was repeated every three or four hours. Clinical improvement was striking. The vital capacity and maximum breathing capacity increased in the majority of cases.

Neo-Synephrine is an effective vasoconstrictor of the mucous membrane of the tracheobronchial tree but a poor bronchodilator. Refractiveness to it does not occur. Epinephrine serves as an effective bronchodilator. The combined effect relieves bronchial spasm and loosens tenacious mucus. As a rule following such therapy the patient coughs and raises mucus and sputum that previously he could not expectorate. Subjective improvement follows, and frequently the obstructive asphyxial picture is relieved after plugs are brought up from the tracheobronchial tree.

This type of therapy is of greatest value in status asthmaticus. It should be used, however, in all types of respiratory disease in which the mechanical factor of obstructive dyspnea due to plugging or spasm of the tracheobronchial tree exists. Untoward results from such therapy are extremely uncommon. If the patient is too ill to be removed from the tent or hood, the nebulizer can be passed through the tent opening or hood sleeve directly into his mouth.

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Based largely on the work of Barach and his associates, physiologically directed therapy in the management of patients ill with obstructive respiratory disease of varied etiology has been well established. A similar program was offered successfully in a series of desperately ill patients. Repeated bronchial relaxation was accomplished, whenever indicated, by the use of rectal aminophyllin, dilaudid, iodides, nebulization therapy with Neo-Synephrine and epinephrine, and proper humidification. High concentrations of oxygen and of helium and oxygen mixtures were given, with and without positive pressures as indicated, through the new Barach-Molomut mask and rebreathing hood apparatus. The patients were critically ill and moribund at times before therapy was started. The sole criterion for successful therapy was objective and subjective evidence. The condition of the patients did not permit more definite studies.

The present report covers the first 4 patients treated. The above therapy in part or in entirety has been employed in a larger series of varying cardiorespiratory diseases and will be reported in other communications.

The first patient was desperately ill with an asphyxial obstructive type of status asthmaticus; the second patient with a virulent bilateral miliary type of virus pneumonia with progressive anoxemia, dyspnea and pulmonary edema; the third patient with a bilateral virus pneumonia with underlying bronchial asthma, complicated by a massive atelectasis of the right lower lobe with mediastinal shift; and the fourth patient with a Type 7 pneumonia involving practically all the lung tissue, septicemia, a toxic type of auricular fibrillation and other complications. Progressive dyspnea, anoxemia and cyanosis had occurred in spite of the conventional methods of therapy.

The program of physiologically directed therapy was begun only after all other methods had failed and the patients were desperately ill. In the 3 pneumonia patients the improvement was progressive over a period of two to five days. The diminished toxicity was striking after the third or fourth day. The anoxemia, cyanosis and dyspnea were controllable almost from the outset of therapy. The usual troublesome cough in the 2 virus pneumonia patients was controlled successfully with supplemental inhalational therapy. Pulmonary decompensation was effectively controlled and convalescence was much more rapid than expected if one were to judge solely by the severity of the clinical picture.

Case Reports

Case 1. The patient, a 35-year-old physician, had been well, except for seasonal hay fever and frequent mild upper-respiratory infections, until November 10, 1942. On that date he complained of rhinorrhea, headaches, chilliness, vague muscular aches and pains, and abdominal discomfort. These symptoms progressed during the following 5 days. On November 15 he complained of a slight cough associated with tightness through the chest and some difficulty in breathing, largely in the expiratory phase. The dyspnea soon became more marked, with characteristic asthmatic wheezing. From November 17

to 19 the dyspnea and wheezing increased in severity in spite of barbiturates, adrenalin and intravenous aminophyllin. The chest remained fixed in inspiration and was emphysematous; over it, inspiratory and expiratory wheezes were heard, with occasional moist rales at the bases. The picture soon became that of the cyanotic, asphyxiated, obstructed, asthmatic patient.

The patient was admitted to the hospital on November 19. During the following 24 hours he was given repeated sedatives, adrenalin, aminophyllin, and helium by nasal catheter. In spite of these procedures he suffered three severe attacks of bronchospasm with an intense obstructive asphyxial picture. His condition was desperate. On November 21 he was placed in a helium-oxygen hood rebreathing apparatus and was given a mixture of 80 per cent helium and 20 per cent oxygen under positive pressure. This proved to be the turning point in therapy and the patient was soon able to get his first rest. He remained in the hood for 2 days. This therapy was further supplemented by the intermittent inhalation of mixtures of 1 per cent Neo-Synephrine and 1:100 epinephrine with 100 per cent oxygen. In addition he received dilaudid, aminophyllin by the rectal route, and supportive intravenous saline and glucose.

Under this program the patient soon improved. His cough became productive of large plugs of mucus. The dyspnea, cyanosis and anoxemia were properly controlled by varying the helium and oxygen percentages. The lung fields cleared progressively. A chest film taken on November 23 suggested emphysema, a plugged bronchus on the left and a mediastinal shift toward the right. After a few days the patient was able to get along without further helium therapy, but the inhalation sprays were continued for 3 days.

The patient was discharged from the hospital on November 29. The lung fields were clear throughout but hyper-resonant. The white-cell count and the percentage of eosinophils were still elevated, however. During the following 10 days at home he continued to complain of intermittent rhinorrhea and mild attacks of tightness through the chest, with slight wheezing. This was usually accentuated by overexertion and exposure to cold, dust or tobacco smoke. A repeated chest film was essentially normal except for slight emphysema and accentuated bronchial markings. The final diagnosis was acute upper-respiratory infection and status asthmaticus with intense dyspnea, anoxemia and cyanosis.

Comment. This desperately ill patient recovered under a physiologically directed program consisting of helium-and-oxygen mixtures under positive pressure, and inhalational sprays of Neo-Synephrine and epinephrine with oxygen. The relief from the dyspnea and anoxemia was most striking from the outset of this program.

CASE 2.* The patient, a 35-year-old, unmarried woman with an uneventful past history, became ill on December 2, 1942. At onset she complained of aches and pains, malaise, shaking chills and fever. During a 10-day period at home persistent cough, fever up to 105°F., progressive cyanosis and dyspnea characterized her course. There was no chest pain or rusty sputum. In spite of the giving of oxygen by facial mask and sulfadiazine, difficulty with respiration and anoxemia progressed. The patient was seen by Dr. Maxwell Finland in consultation and removal to the hospital was advised.

*This case is reported through the courtesy of Dr. Maxwell Finland.

On admission on November 12, the patient was acutely ill, dyspneic, dehydrated, drowsy, incoherent and cyanotic. The temperature was 101°F., the pulse 120, and the respirations 30. The respiratory movements were rapid and shallow. The lungs revealed a variety of expiratory squeaks and medium to coarse rales, largely limited to the top of both lungs anteriorly and the lower half of both lungs posteriorly. The abdomen was distended and the urinary bladder full. The white-cell count was 16,200, with 86 per cent polymorphonuclear leukocytes and many toxic granules. The red-cell count was 4,460,000 and the hemoglobin 65 per cent.

The admission diagnosis was bilateral atypical pneumonia. Chemotherapy was discontinued, and oxygen was given by nasal catheter and later by mask, and fluids by clysis and general supportive care. A sputum culture later showed many colonies of staphylococci by direct inoculation on blood agar. Sulfadiazine was resumed on December 16. An x-ray film revealed a bilateral, diffuse, miliary type of virus pneumonia.

During the 1st week in the hospital the patient's course was characterized by progressive dyspnea, cyanosis, abdominal distention and periods of irrationality and urinary incontinence. The temperature remained between 101 and 103°F., the respirations at 48 and the pulse at 120 to 140. On the 16th day of illness the patient's condition was desperate and a program of positive pressure with oxygen and helium-oxygen mixtures was finally begun.

For 15 hours a B. L. B. mask was arranged to give positive pressure in the expiratory phase of respiration, with flows of 10 to 12 liters per minute of oxygen or helium-oxygen mixtures. The respiratory rate was slowed and the patient managed to get a few hours of rest during the first night. On December 19 a new Barach mask metered for positive pressure was used and this was continued for 5 hours. The patient was then placed in a helium-oxygen hood. It is significant that the respirations had dropped to 28 before entering the hood, and that gurgling and bubbling rales heard over the top of both lungs cleared up promptly with positive pressure.

The patient remained in the hood for 3½ days, and had her first hours of comfortable sleep there. During this time she received mixtures of helium and oxygen in varying percentages depending on the anoxic or obstructive factor. In addition she received inhalational sprays of mixtures of 1 per cent Neo-Synephrine and 1:100 epinephrine every 4 hours, with flows of oxygen of 4 to 6 liters per minute. The mixture was generally introduced through the sleeve of the hood, with the nurse holding the nebulizer in the patient's mouth or the patient holding the nebulizer between her lips. Further therapy consisted of 1/64 gr. of dilaudid twice daily as needed, and potassium iodide orally. The abdominal distention was strikingly relieved at the onset of therapy when the patient received straight oxygen. Sulfadiazine was stopped on December 20 because of diminished urinary output. At various times definite prolonged expiratory wheezes were elicited over both lung fields.

The general course was one of slow but progressive improvement. While the patient was in the hood the temperature ranged around 99.6°F. rectally, the pulse between 96 and 112, and the respirations between 28 and 32. She was considerably less toxic. Her color remained pink and breathing was not labored.

The cough soon became productive. The sputum was at first sticky and glairy, and later less tenacious. After 3½ days in the hood she returned to the Barach–Molomut mask with positive pressure of 4 cm. in the expiratory phase only, using largely 95 per cent oxygen alone. This was continued for 2 days and thereafter intermittently for 6 days. During these periods the percentage of oxygen was slowly reduced. Nebulization therapy was continued, however, until December 31. Scattered medium moist rales could still be elicited at the bases posteriorly on January 2, 1943, the day the patient was allowed up in a chair. She shortly became ambulatory and was discharged home to convalesce on January 5. During the first 2 weeks at home she had two attacks of sudden breathlessness at night, relieved by Propadrine Hydrochloride. Scattered expiratory wheezes could be elicited. This bronchospasm soon cleared up however.

Comment. A desperately ill patient with bilateral virus pneumonitis, unresponsive to usual methods of care, responded characteristically to a program of physiologically directed inhalational therapy consisting largely of mixtures of helium and oxygen under positive pressure. The most striking observation was the relief from cerebral anoxemia and respiratory failure which appeared imminent at the beginning of therapy.

Case 3.* The patient, a 25-year-old intern with a past history of autumnal asthma, was admitted to the hospital because of a 4-day history of sore throat, headache, malaise, anorexia, abdominal distress, fever, substernal tightness and nonproductive cough.

Physical examination revealed a flushed, perspiring young man with slight expiratory wheezing. The temperature was 101°F., the pulse 86, and the respirations 24. The outstanding findings were in the chest, which was increased in the anteroposterior diameter, with the breath sounds distant. There was slight dullness at both bases, with bronchovesicular breathing but no rales. Inconstant wheezes were heard throughout both lung fields. A chest film revealed haziness in the right-lower and left-lower lung fields.

The laboratory data revealed a slightly elevated white-cell count. Throat, sputum and blood cultures were negative for pneumococci.

The diagnosis on entry was an atypical pneumonia. The patient was treated symptomatically. In the course of the first few days the temperaure rose to between 102 and 104°F. On the 6th day, because of failure to respond and because of increasing signs of consolidation, he was given full doses of sulfadiazine. Nevertheless, there was a gradual rise in pulse and respiratory rate, and no drop in temperature. Paroxysms of nonproductive coughing then developed, accompanied by cyanosis and exhaustion. Both the clinical and x-ray impressions were those of an extensive pneumonitis involving the entire right lung and the left lower lung. The mediastinum was shifted to the right, and there was apparently some degree of atelectasis of the right lower lobe. At times there was definite evidence of bronchospasm, only partially relieved by epinephrine.

The clinical course was progressively downhill, with increasing anoxemia, cyanosis and dyspnea in spite of oxygen therapy with the B. L. B. mask and oxygen tent. On December 27, the patient appeared desperately ill. Loud, bubbling rales were heard throughout both sides of the chest in both phases of respiration, with marked lengthening of expiration. A program of therapy was begun consisting of nebulizer inhalations of epinephrine and Neo-Synephrine, rectal aminophyllin and positive-pressure helium-oxygen mixtures. Within 15 minutes after the patient was placed in the hood under positive pressure the bubbling rales disappeared and the respirations became easier. He soon fell asleep and awoke in an hour considerably refreshed.

He remained in the hood for 4½ days. Nebulization was generally carried out while in the hood. The mixtures of helium and oxygen varied depending on the degree of cyanosis and respiratory obstruction. The toxicity diminished strikingly and the temperature began to return to normal after the 3rd day. The pulse and respiratory rates became slower shortly after this program of therapy was begun. The troublesome cough was more easily controllable, less distressing and more productive. After residence in the hood the patient was placed in the Barach–Molomut mask with varying percentages of oxygen under positive pressure. These percentages were gradually reduced, and oxygen therapy was stopped on January 1, 1943. Nebulization therapy was continued for a few more days. He was permitted up on the 24th hospital day and was discharged home on the 30th day. The final diagnosis was bilateral atypical pneumonia with atelectasis of the right base and a mediastinal shift to the right, and acute bronchospasm.

Comment. A seriously ill patient unresponsive to the usual methods of care, responded characteristically to a program of inhalational therapy consisting largely of mixtures of helium and oxygen under positive pressure.

Case 4.† The patient, a 44-year-old, married man, had had a chronic upper-respiratory infection for 1 month prior to the present illness. Three days before hospital entry there occurred the sudden onset of marked malaise, repeated chills with high fever, cough productive of blood-streaked sputum and pleuritic pain in the right lower chest. In the past a mild hypertension and renal lithiasis had been observed.

The admission physical examination revealed a markedly dyspneic, cyanotic, toxic and dehydrated middle-aged man. The temperature was 104°F., the pulse 120, and the respirations 30. There was dullness at both lung bases, with diminished breath sounds and moist rales. The cardiac examination revealed no murmurs or enlargement. The rhythm was regular. The blood pressure was 140/70. The laboratory examination revealed a Type 7 pneumococcus in the sputum and also in the first blood culture. The white-cell count was 17,700, with 82 per cent polymorphonuclear leukocytes. The hemoglobin level and red-cell count were within normal limits. A urine examination was entirely negative and showed a specific gravity of 1.029.

The admission diagnosis was lobar pneumonia and septicemia due to a Type 7 pneumococcus. The patient was started immediately on 4 gm. of sulfadiazine, with 1 gm. every 4 hours thereafter. During the first 4 days the temperature varied between 102 and 104°F., the pulse between 110 and 130, and the respirations between 25 and 30. On the 5th day the temperature climbed to 105°F., the pulse to 150, and respirations to 40. X-ray studies revealed an extension of the process from the right base to the right upper lobe. The blood sulfadiazine level

*This case is reported through the courtesy of Drs. Harry Linenthal and H. L. Blumgart.

†This case is reported through the courtesy of Dr. Hyman Morrison.

was 9.0 mg. per 100 cc. The patient was extremely anoxic and demonstrated a moderate degree of expiratory stridor in spite of oxygen therapy with both B. L. B. and Barach–Eckman masks. He was then given a Type 7 antipneumococcus serum — 150,000 units on the 1st day and 270,000 units on the 2nd day. Because of the persistence of anoxemia, cyanosis and mental confusion and the appearance of respiratory fatigue, a program of positive-pressure oxygen was agreed on. The patient was first placed in the hood rebreathing apparatus, with 100 per cent oxygen under positive pressure of 2 to 5 cm. of water. He remained in the hood most of the time during the following 4 days. During the rest of the time this program was continued in the Barach–Molomut mask. The temperature fell gradually during these 4 days and the respirations were much less labored. Cyanosis and anoxia were much less evident. However, auricular fibrillation developed with a radial rate of 150. The white-cell count rose to 56,000, urine examinations revealed albuminuria with a fixed specific gravity of 1.010, and the nonprotein nitrogen rose to 81 mg. per 100 cc. The patient presented signs of upper abdominal distention, which was relieved with a Levine tube and gastric lavage. Positive-pressure oxygen was discontinued on the 5th day after all signs of respiratory fatigue and tracheal rales had subsided. Oxygen therapy was continued, using the Barach–Molomut mask with mixtures of oxygen varying from 80 to 90 per cent depending on the degree of anoxemia.

The auricular fibrillation was controlled by digitalis. Because of the findings of renal insufficiency, chemotherapy was omitted. During the next week the temperature again began to rise slowly in a fluctuating fashion, reaching 103°F. X-ray examination revealed persistence of signs in the right upper and middle lobes. The white-cell count gradually dropped to 14,000 and the nonprotein nitrogen fell to 61 mg. per 100 cc. The urine showed persistent albuminuria, with specific gravities averaging 1.010. In the terminal 5 days progressive disorientation and confusion developed. Because of the cerebral symptoms it was thought advisable to continue the oxygen therapy in the oxygen tent. During the last 24 hours in spite of this therapy the patient developed rapid pulmonary edema and respiratory failure and died on January 31.

The autopsy revealed massive bilateral pneumonic involvement, with bronchiectatic abscesses in the right base, diffuse fatty infiltrative changes in the renal tubules and an acute bacterial endocarditis (terminal, Type 6 pneumococcus).

Comment. A desperately ill 44-year-old man with a Type 7 pneumonia and septicemia developed progressive signs of anoxemia, cyanosis and respiratory fatigue in spite of the usual methods of oxygen administration. These were adequately controlled during a 4-day period with a program of positive-pressure oxygen. However, progressive signs of renal insufficiency, cerebral psychosis and pneumonia spread and acute bacterial endocarditis resulted in death.

Summary

A report is made of the use of positive-pressure inhalational therapy with mixtures of helium and oxygen and oxygen alone in the treatment of 4 patients desperately ill with respiratory disease.

The importance of supplemental inhalational therapy of mixtures of Neo-Synephrine and epinephrine, vaporized with a continuous flow of oxygen, is demonstrated.

Helium-oxygen and oxygen mixtures under positive pressure have a definite value in the therapy of pulmonary edema of varied etiology, bronchial asthma, acute bronchiolitis, acute fibrinous tracheobronchitis, severe emphysema, pulmonary fibrosis, laryngospasm, laryngeal diphtheria with obstruction, severe obstructive whooping cough and certain pneumonias or gas poisonings.

All cases of obstructive respiratory disease demonstrating anoxia, cyanosis, asphyxia, pulmonary edema or progressive intractable dyspnea, alone or in combination should have a trial with the above therapy.

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TOXIC PSYCHOSIS AND DEATH ASSOCIATED WITH POTASSIUM THIOCYANATE THERAPY*

Report of a Case

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THE purpose of this article is to emphasize the toxicity of potassium thiocyanate and to present a case showing acute psychosis with a fatal outcome.

The literature contains many reports concerning the use of potassium thiocyanate, the most notable early references being those of Pauli[1] in 1903 and 1904, who first noted its hypotensive effect; Westphal[2] in 1926, who reawakened interest in the therapeutic possibilities of the drug; and Barker[3] in 1936, who first emphasized potassium thiocyanate blood levels as a method of control of therapy.

The pharmacologic and therapeutic properties of this drug were first reviewed in 1925 by Nichols,[4] who observed that it was highly toxic for guinea pigs, and that a few hours after administration of the drug there developed diarrhea, progressive loss of weight, marked evidence of spinal irritation, convulsions, coma and death. His experiments appeared to substantiate Bernard's original claim that potassium thiocyanate is a tissue poison.

A total of 9 fatalities have appeared in the literature. The first fatal case, reported by Lesser[5] in 1898, was that of a magician who took the drug with suicidal intent. Death occurred within ten hours, and an autopsy revealed extensive necrosis and hemorrhage in the mucous membrane of the gastrointestinal tract. The second case, reported by Kobert[6] in 1906, was that of a woman who died twenty-eight hours after ingestion of this drug. There is some hesitancy in including this among the lethal group because of the inordinately small total dose of the drug allegedly taken (5 gr.). In 1916, Vintilesco and Popesco[7] reported a toxic psychosis with delirium, convulsions, spinal rigidity, coma, anuria and death in two days after the intake of an estimated 100 gm. of potassium thiocyanate. Healy[8] in 1931 reported 2 cases in each of which the patient had taken a total of 9 gm. of potassium thiocyanate for therapeutic purposes. In one case the lowering of the blood pressure was followed by marked weakness, collapse, semicoma and death nineteen days after discontinuance of the drug. In the other case death occurred two weeks after discontinuance, following a similar train of symptoms. Goldring and Chasis[9] mentioned 2 additional fatal cases, again associated with the therapeutic administration of potassium thiocyanate. In these cases there was an acute outbreak of mental symptoms, particularly confusion, incoherence, hallucinations and delirium, followed by excessive psychomotor activity, anuria and death. The last 2 cases reported were those of Garvin[10] and Russell and Stahl,[11] both with pictures of toxic psychosis, overactivity and death. The latter authors emphasized the following characteristic clinical syndrome in mortal cases: first, there may be weakness (possibly due to lowering of the blood pressure), then outbreak of an acute toxic psychosis that primarily presents delirium, confusion, hallucinations and signs of irritation of the central nervous system. In all cases in the literature death has occurred within nineteen days after the onset of the first symptoms. It is to be noted that the two blood levels recorded in association with the fatal cases were only 18.7 mg. and 21.6 mg. per 100 cc., and that in 1 case the total drug ingestion was as little as 5.6 gm., the patient receiving only 0.4 gm. (6 gr.) per day for fourteen days.

Although it is quite clear that in fatal cases symptoms of mental disorder are prone to precede exodus, mental symptoms in the course of potassium

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thiocyanate therapy are by no means limited to fatal cases. Toxic central-nervous-system symptoms have been stressed from the earliest days of the use of the drug. McNeill[12] (1933), using it for the reduction of hypertension in state-hospital patients, noted in 4 out of 12 cases unsteady gait, confusion and rambling talk resembling that of an acute alcoholic intoxication. The mental reaction lasted for four to eight days after withdrawal of the drug. In 11 of 50 cases treated by Goldring and Chasis,[9] the usual order of toxic symptoms was muscular fatigue associated with nausea, vomiting, disorientation and mental confusion, then frequently motor aphasia and hallucinations of sight and hearing. In ambulatory cases, they noted that the muscular fatigue was first complained of, but in bed patients this early warning of toxicity might pass entirely unnoticed, and it was not unusual for motor aphasia, mental confusion and even hallucinations to be the first sign of potassium thiocyanate intoxication. These authors believed that the toxicity was not especially a function of the dosage used. Other writers have stressed the fact that there may be markedly varying rates of excretion of potassium thiocyanate in different patients. Some are distinctly susceptible, and in some there is little or no margin of safety between the therapeutic and the toxic dose. Blood levels afford comparative safety in the control of therapy, yet cases have been reported of toxicity at supposedly safe levels (8 to 12 mg. per 100 cc.).

With regard to the manner in which potassium thiocyanate exerts its effects on tissues, the experiment of Robinson and O'Hare[13] is noteworthy. By use of the Warburg apparatus, it was found that slices of liver exposed to potassium thiocyanate in a serum medium suffered a reduction of oxygen consumption of 40 per cent when the potassium thiocyanate concentration was 20 mg. per 100 cc. They suggest that there is probably a continuous moderate reduction of metabolism in all tissues. It is possible that nervous tissue and kidney tissue — in view of uremic exodus in several cases — are especially vulnerable.

Case Report

W. S., a 46-year-old, married Negro, was admitted to the Boston Psychopathic Hospital on September 30, 1942, because of delusions and confusion. From the end of World War I, in which he saw military service, until his illness, he was employed as a letter carrier. He was known as a hard, steady worker and had no bad habits. Except for "pleurisy" of short duration each winter, he had been essentially without complaints.

In the spring of 1940, however, the patient was admitted to a hospital for the first time because of progressive dyspnea, chest pain and loss of weight of several months' duration. Physical examination at that time revealed essentially a well-developed individual, moderately obese but not acutely ill. There was an arcus senilis arteriovenous nicking of the retinal vessels, elevated blood pressure (210/130) and slight cardiac enlargement, both clinically and by x-ray. An electrocardiogram strongly suggested coronary thrombosis with myocardial infarction. Laboratory analysis revealed normal blood, a nonprotein nitrogen of 40 mg. per 100 cc., a negative urine and adequate renal function by a dye-excretion test (phenolsulfonephthalein). On bed rest and digitalization, the patient improved and after 1 month's hospitalization was discharged with a diagnosis of hypertensive arteriosclerotic heart disease.

For 2 years the patient was well and able to continue with his work, but in August, 1942, he again complained of shortness of breath, aggravated by exertion, and was readmitted to the hospital. At that time he was coughing, with production of occasional brownish sputum, and the left lower chest showed dullness. There was no peripheral edema. The blood pressure was 242/140. The heart was enlarged to the right and left as shown by x-ray, and an electrocardiogram revealed evidence of an old anterior-wall infarction. The blood was normal, and serologic tests for syphilis were negative. Urine examination showed persistent albuminuria (30 to 50 mg. per 100 cc.) and a low specific gravity (1.008 or less) on random specimens. The nonprotein nitrogen was 45 mg. per 100 cc.

The patient was put to bed. On August 14, potassium thiocyanate therapy was begun, 3 gr. three times a day, and a blood level of 8 to 9 mg. per 100 cc. was subsequently obtained. One and a half grains of digitalis three times a day was given for three days, followed by 1½ gr. daily. There was gradual disappearance of the cough and brownish sputum, and improvement of the dyspnea. On September 23, the 40th day of treatment, the patient was allowed out of bed. The blood pressure all this time had maintained itself around 210/130. On September 25, the potassium thiocyanate was discontinued. On September 30, the patient developed delusions that he was being shunned by everyone and was being threatened. He wandered about looking for a gun to protect himself. He was violent, overactive and disoriented and was transferred the same day to the Boston Psychopathic Hospital.

The mental status revealed an inattentive, perplexed, preoccupied patient who stared about in bewilderment. He gave his family history fairly coherently but was unable to tell the year of his marriage, the ages of his sons or what he had recently eaten. He could not give the date or the name of the hospital. He had no memory of the events that had led to his admission. His retention of digits was exceedingly poor, and his range of general information was inadequate.

About 12 hours after admission, the patient began to wander about the ward praying loudly and fervently, and exposing himself. He became resistive and combative and failed to grasp the significance of his surroundings. On October 2, blood studies revealed that the potassium thiocyanate level was 18.9 mg. per 100 cc. and the nonprotein nitrogen 70 mg. During the next few days the patient went rapidly downhill, showing excessive psychomotor activity and requiring constant restraint. He developed coma and increasing uremia. On October 8, at which time the potassium thiocyanate level was 24 mg. per 100 cc. and the nonprotein nitrogen 130 mg., he suddenly died. Death occurred on the 55th day after

the beginning of potassium thiocyanate treatment, 14 days after the drug was discontinued, and 9 days after the onset of mental symptoms. The total amount of the drug administered was 25 gm.

Comment

Essentially, this patient had a past history of hypertension and two episodes of congestive failure requiring hospitalization. On the second hospitalization, it was evident that he had developed albuminuria and a low urinary specific gravity. After several weeks he was sufficiently improved to be up and about. He had received treatment with potassium thiocyanate for forty-two days and it was then omitted because of his improvement. Five days later, however, he suddenly developed a toxic psychosis, went downhill rapidly, showed excessive psychomotor activity and died in uremia. Potassium thiocyanate levels taken two days after the onset of psychosis were elevated beyond the therapeutic range.

In cardiovascular renal disease, death from uremia is not uncommon. In this case the patient was markedly improved with treatment but suddenly took a dramatic turn for the worse. This course of events may conceivably occur in uncomplicated cardiorenal disease, but it seems quite likely that in the present case potassium thiocyanate intoxication played a significant part in the slump and ultimate death. This is also suggested by the sudden appearance of toxic psychosis while the patient was presumably getting well, and by the marked resemblance of the whole picture to that observed in cases of potassium-thiocyanate intoxication described in the literature. This syndrome some authors regard as characteristic of fatal poisoning. It is difficult to evaluate the exact part played by the potassium thiocyanate, and indeed it is possible that several factors are operative, including the renal impairment, elevated potassium thiocyanate blood level and special tissue vulnerability. There is not yet full understanding of the sudden elevations in the blood levels of potassium thiocyanate that can occur not only in patients who receive constant doses of the medication, but even — as in this case — after the drug has been discontinued.

In view of the experience thus far, it seems important to bear in mind the dangers inherent in the use of potassium thiocyanate and the possibility of fatality if the drug is used in the presence of renal impairment. Acute psychosis in the course of treatment should also be regarded as a danger signal.

Summary

A case of acute toxic psychosis and death associated with potassium-thiocyanate treatment of hypertension is described, being the tenth case of this type to be reported in the literature.

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MEDICAL PROGRESS

REGIONAL ANESTHESIA*

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IN THE current progress of regional anesthesia three new developments are outstanding. They are continuous caudal anesthesia for obstetrics, the subarachnoid injection of ammonium sulfate for the relief of intractable pain and refrigeration anesthesia (crymoanesthesia). However, because the anesthesiologist of today is interested in many things other than merely rendering patients insensible to pain during an operation, sections on new drugs, local anesthesia, spinal anesthesia, supportive treatment, complications and military anesthesia are included in this report.

CONTINUOUS CAUDAL ANESTHESIA

The idea of painless childbirth has been an enchanting one to anesthetists as well as to mothers since the introduction of chloroform. Continuous caudal anesthesia is the latest method holding forth this promise to appear on the anesthesia horizon. Manalan,[1] in August, 1940, introduced a technic that could have been but was not used for the continuous production of caudal anesthesia. He inserted a 13-gauge needle in the sacral hiatus and passed a No. 4 nylon ureteral catheter in through the needle, withdrawing the latter and leaving the catheter in place. After labor had progressed to the point that caudal anesthesia was needed, he injected 30 cc. of an anesthetic solution through the catheter into the sacral cavity and withdrew the catheter.

Hingson, Southworth and Edwards,[2-4] impressed with the possibility for the use of the equipment described by Lemmon[5] for continuous spinal anesthesia, adapted this apparatus (a malleable needle, tubing and syringe connected by Luer-Lok connections) for the production of continuous caudal anesthesia for obstetrics. The type of needle has been changed as dictated by their experience, as some of the original needles broke in situ. Adams and his co-workers[6] have reported the use of a ureteral catheter by the method described by Manalan to obviate the possibility of breaking needles and to inject their agent through the catheter to produce continuous anesthesia. Several years after this method has been given a critical trial in institutions throughout the country, a worth-while evaluation of its place in obstetrics will be forthcoming. Any attempt at this stage of development to apply continuous caudal anesthesia routinely in all obstetric cases is apt to bring about some undesirable results. Southworth, Edwards and Hingson[7] point out the possibilities of this method in certain types of general surgery, as well as in obstetrics.

RELIEF OF INTRACTABLE PAIN

Rovenstine and Wertheim[8] make a plea for anesthetists to familiarize themselves with the various nerve blocks to provide pain relief for patients suffering from trigeminal, brachial-plexus and cervical-plexus neuralgia, sciatica, coccygodynia and shoulder pain. They advocate alcohol block of the sympathetics by the paravertebral route for angina pectoris and thrombophlebitis. Sensory-nerve block with alcohol for pain relief in inoperable carcinoma has been extremely worth while in their hands. These procedures are done only after medical treatment has failed to relieve pain or when surgical transection of sensory pathways is considered a grave hazard. Allen and Tuohy[9] report that somatic pains can be successfully relieved in many cases by local anesthetization.

Bates and Judovich[10] in an attempt to relieve intractable pain have administered 3000 injections of ammonium-salt preparations by the paravertebral route and by local infiltration. Starting with an extract of the pitcher plant (*Sarracenia purpurea*), the active principle of which they concluded was the ammonium ion, they now use ammonium sulfate. At present they inject it subarachnoidly in an attempt to control all types of intractable somatic pain. They state: "Intraspinal ammonium sulfate did not yield satisfactory results in the so-called 'pre-metastatic' phase of malignancy. The complaints of burning, urgency, tenesmus and other pains of this period were not relieved." At the time of injection, severe pain is experienced in the area supplied by nerves bathed by this solution. This can be eliminated, they state, by preceding the injection with 50 mg. of procaine hydrochloride, which provides a short period of spinal anesthesia.

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Hand[11] used ammonium sulfate subarachnoidly by the method described by Bates and Judovich in an attempt to relieve 48 patients of their intractable pain. Thirty-two of these patients had metastatic malignancy, and in 16 the treatment was successful. Six of 7 patients suffering from painful spinal-cord arachnoiditis had relief of pain. Four patients who had become addicted to morphine before treatment was instituted and 4 additional patients whose pain was finally thought to be on a functional basis received no relief. Hand thought that the major difficulty with this procedure was the inability to predict the outcome of the treatment before it was instituted, since he found it impossible to differentiate somatic pain as defined by Bates and Judovich.

Three minor complications usually accompany this treatment. First, 70 to 80 per cent of the patients experienced nausea and retching during the induction of anesthesia. This nausea could be relieved or attenuated by intravenous injections of 1/100 gr. of atropine sulfate. Secondly, 50 to 60 per cent experienced a post-spinal headache. Thirdly, 20 to 30 per cent were annoyed by varying degrees of paresthesias over the buttocks and sacrum.

Refrigeration (Crymoanesthesia)

In 1939, after long and careful study of the effects of resistance of peripheral tissue to asphyxia at various temperatures, Allen[12] suggested the possible usefulness of maintaining life processes at a reduced rate by lowering the temperature. Radical chilling of the body had previously been introduced by Fay[13] for the cure of cancer, but he also described dramatic control of infections, including gas gangrene. True refrigeration anesthesia was first used for amputations of partially gangrenous extremities of patients in the older age group. When a tourniquet is applied and the extremity packed in ordinary chipped ice (without salt), the oxygen demands are reduced sufficiently (13 per cent for each degree centigrade) to prevent necrosis for many hours. The skin temperature falls to 2 to 4°C. and surgical anesthesia is complete within about two hours. From the anesthesia standpoint, this is thought to be an entirely new principle, namely anesthesia of protoplasm, in contrast to all former methods, which produce only anesthesia of nerves.[14]

Theoretically, one might expect that the tourniquet and refrigeration would increase the dangers of postoperative slough. Practically, it has been found that the factors of safety in this respect are quite adequate even in the presence of arterial disease. One report of 58 amputations done with this type of anesthesia gave the following as its benefits: ease and quickness of operation, absence of pain both before and after operation, inhibition of infection, conservation of poorly nourished tissues, control of edema, promotion of drainage when necessary, probable reduction of thrombotic and embolic dangers and, pre-eminently, the avoidance of shock.[15, 16]

McElvenny[17] used intensive refrigeration without a tourniquet to control pain, to prevent infection and to overcome shock in a patient who had bilateral traumatic leg amputations.

Refrigeration anesthesia seems to offer advantages for nearly all cases of severe wounds of the extremities. Prevention and treatment of shock may be sufficient indications; surgical anesthesia is a valuable by-product. It has been advocated for use in combat areas by military surgeons to relieve the suffering and blood loss from periodic loosening of an emergency tourniquet.[18]

New Drugs

In 1939, Eisleb and Schaumann[19] introduced a new synthetic phenyl-piperidine derivative, Demerol (1 methyl, 4 phenyl-piperidine, 4 carboxylic acid ethyl hydrochloride), which was found to possess properties similar to those of atropine and morphine. Since then numerous European investigators have attested to the drug's usefulness in the therapy of pain.[20] Batterman[21–23] studied the analgesic effectiveness, potency and safety of Demerol, and concluded that it could be used for patients who would ordinarily require opiates. He found the drug similar to morphine in its analgesic action and approaching it in effectiveness, but with less depression of the central nervous system. Unlike morphine, depression of the respiratory rate and urinary retention are rare following therapeutic doses. The size of the pupils and the pupillary reflexes are not affected, and in recumbent subjects there is no appreciable alteration in blood pressure, ventricular rate, electrocardiogram or basal metabolic rate.

Climenko and Berg[24] in a study of the influence of Demerol on the contraction of the ureter concluded that it inhibits the amplitude of contraction and diminishes the tonus of the ureter.

Rovenstine and Batterman[20] studied this drug to evaluate its effectiveness as a preanesthetic agent in man and to determine the differences between its action and that of morphine. They concluded:

> [Demerol] will provide psychic sedation not surpassed by morphine; will not depress respiration or other vital functions to the same degree as will comparable amounts of morphine; will facilitate induction of anesthesia as does morphine; is more effective in

drying secretions than morphine; has fewer unfavorable side effects, such as nausea and vertigo, than morphine; and will reduce the amount of anesthetic agent required to produce the optimal degree of narcosis to the extent that can be obtained with morphine.

In 1937, the synthesis of monocaine hydrochloride (mono-isobutyl-aminoethyl-para-aminobenzoate hydrochloride), an isomer of procaine, was reported by Goldberg and Whitmore,[25] who claimed that it was a good local anesthetic with pressor action and synergistic with epinephrine. They also stated that a 1 per cent concentration could be used without the addition of epinephrine. After extensive investigation designed to test the local anesthetic efficiency of monocaine, its possible direct vasoconstrictor power, its local and systemic toxicity and its effects on vital function, Schamp, Schamp and Tainter[26] reported the following:

> These results taken together indicate that the local anesthetic efficiency of monocaine is similar to that of procaine quantitatively and qualitatively, as is also the systemic toxicity, except for a greater cardiovascular paralyzing action of monocaine. They also fail to substantiate current claims that monocaine is a pressor agent, or that it potentiates the action of epinephrine. Since monocaine is definitely more irritating to tissues than procaine, it lacks the advantages which would justify its selection over procaine as a local anesthetic for injection purposes.

The formic acid salt, monocaine formate, which is soluble in any dilution needed clinically, was used by Burdick and Rovenstine[27] for a clinical study of the drug as a spinal anesthetic agent. They used technics for administration commonly employed for spinal anesthesia with procaine, dissolving the monocaine formate crystals in the spinal fluid to make concentrations of 2.5, 5.0, 7.5 and 10.0 per cent. Diffusion of monocaine was found to differ from that of procaine in the spinal fluid, and the level of sensory anesthesia sometimes continued to extend cephalad for as long as thirty minutes. "With the amounts used, 50 to 150 mg. in 5 per cent concentration in spinal fluid, the results observed during anesthesia and postoperatively indicate that complications are no more severe and of lower incidence than might be expected from procaine." In conclusion, they expressed the belief that monocaine is a safe, useful agent for spinal anesthesia when given in low concentration and in small or moderate doses.

Local Anesthesia

Beutner and Calesnick[28] carried out experimental research to find the physiologic and chemical properties possessed by many of the widely used local anesthetics. They concluded that efficient local anesthetic agents have so far been obtained only as ester compounds of benzoic acid, aminobenzoic acid or some related substituted benzoic acid (Nupercaine, quinolin carbonic acid, used in one instance). These acids are combined with some amino alcohol or a related compound (for Nupercaine, one having a diamino radical) that supplies the basic property. The ester-like loose combination between the acid and the amino alcohol is the essential indispensable characteristic.

Physiologically all efficient local anesthetics have been found to be convulsants and stimulants of the cerebral cortex, the convulsive power being approximately parallel with the efficiency of the local anesthetic agent.

Apparently it is more than a casual coincidence that all efficient local anesthetics are convulsants. They must possess a marked affinity to the nerve cells in order to depress selectively the terminal nerve fibers without injuring the cells.

Mousel,[29] Tuohy,[30] Adams[31] and Seldon and Lundy[32, 33] have recently published timely and worth-while papers covering the commoner regional nerve-block technics for all parts of the body. One finds a crystallization of valuable clinical experience in these writings that comes only after years of experience. These articles should be read by all anesthetists interested in the proper application of regional anesthesia in modern anesthesiology.

Much interest has been shown of late in the use of local infiltration and regional block anesthesia for obstetrics.[34-37]

Spinal Anesthesia

Goldberg, Koster and Warshaw[38] write as follows:

> By means of new chemical technics it is shown that procaine within the subarachnoid space remains essentially unchanged. The fall in concentration of procaine, which is responsible for the wearing off of spinal anesthesia, is due to vascular absorption. Once in the blood stream procaine is rapidly hydrolyzed (detoxified) by an enzyme. . . . At no time is there any appreciable trace of procaine in the blood; hence, the cause of various "toxic" effects which have been attributed to a procainemia must be sought elsewhere. . . . Nearly all the injected procaine (90 per cent on the average) is excreted in the urine, but only in the form of products of detoxication.

In a recent study of spinal anesthesia in normal, unoperated man, Smith, Rovenstine and their collaborators[39] have shown that anesthetic denervation does not produce renal hyperemia. Smith[40] has more recently reaffirmed this conclusion after a more complete review of the literature. In the first paper the authors suggested that the arteriolar

bed generally — apart from the skin — possesses considerably more autonomy than is usually attributed to it. They believe that blood pressure may change very little during high spinal anesthesia in normal, unoperated man. For the most part, such decrease as was observed in these unoperated patients was a result of the decrease in the stroke volume of the heart, which they attributed to a decrease in venous pressure.

The extreme falls in blood pressure observed during high spinal anesthesia are believed by Papper, Bradley and Rovenstine[41, 42] to be the result of decreased venous pressure (and hence a decreased cardiac output) following opening of the abdomen and the attendant operative procedures inflicted in the face of vasomotor paralysis and loss of vasomotor defense. Trauma, hemorrhage, anoxia, the weight of metal and other items upon the abdomen, the pressure of packs between the viscera, the position of the patient, malaise, fever and other complicating factors may contribute to the progressive reduction in venous pressure and the ultimate embarrassment of the circulation.

There seems to be a trend toward wider clinical application of spinal anesthesia by anesthetists in general.[43] This appears to be due to increasing confidence in the ability of vasomotor drugs, plus intravenous fluids (saline and glucose solutions, plasma and blood) to combat the hypotension often associated with spinal anesthesia. In addition, certain refinements in technic for spinal anesthesia have given the anesthetist more control over the distribution of the drug in the subarachnoid space.[44, 45]

Fractional (continuous) spinal anesthesia is gaining in favor and seems to have answered a real need where ensured relaxation is needed over long periods for difficult abdominal or orthopedic operations.[46–49] To date there has been a lack of uniformity of opinion concerning the best anesthetic agent to use by this method.

Supportive Treatment

Every effort should be made through the use of supportive treatment to prevent the onset of shock or to institute treatment before the condition has progressed irrevocably. Certain tests may detect shock during its earlier stages when significant changes are noted in the hematocrit, the specific gravity of the plasma and whole blood and the plasma protein level.[50] The benefit of whole blood and plasma transfusion to the patient in shock is beyond question. Elman[51] has shown that a solution of hydrolyzed protein containing amino acids and polypeptides exerts a definite therapeutic effect, as evidenced by prolongation of the survival time, an increase in the amount of hemorrhage that could be sustained and a higher level of blood pressure as compared with that in controls in whom dextrose alone was used or in whom there was no replacement.

Because of the part that tissue anoxia must play in the vicious cycle of shock, it is interesting to note the favorable effect of administering high oxygen concentrations reported in two recent papers.[52, 53] Others[54] report that the course of events in hemorrhagic shock is in no way altered when venous anoxemia is prevented by administering oxygen at high pressure.

Beecher, McCarrell and Evans[55] have confirmed the observations of Seeley, Essex and Mann[56] that shock produced in dogs by exposure and manipulation of the intestine is slower to appear when barbiturate (sodium amytal) anesthesia is used than when ether anesthesia is employed. However, they found no significant delay in the onset of shock produced by hemorrhage when barbiturate anesthesia was used. Their observations together with those of Parsons and Phemister[57] and Blalock,[58] who found similar effects under barbiturate and ether anesthesia when shock was produced by muscle trauma, indicate that barbiturate as compared with ether anesthesia is not useful in delaying all types of shock.

Studies have been made by Seligman and Fine,[59, 60] using a radioactive plasma protein, to test the prevailing opinion that an increased permeability of the capillaries exists in shock and that a subsequent loss of plasma into the tissues ensues, so that the effective circulating-blood volume falls to a level incompatible with life. They found that, whereas the integrity of the capillaries may be impaired in the latent shock phase, there is no evidence of the significant loss of plasma into the tissues in untreated fatal shock following hemorrhage.

Infusion of blood and other fluids through the bone marrow, as advocated by Tocantins,[61, 62] gives another route by which large amounts may be administered. This method is particularly applicable in pediatrics, since transfusions to children under the age of two years are difficult to give by vein. It is also important in adult patients whose bodies are widely burned or whose veins are thrombosed. These intramedullary infusions are injected into the bone marrow of the manubrium sterni in adults and into the tibia or femur in infants. Doud and Tysell[63] were able to inject 9025 cc. of blood and 13,155 cc. of fluid into the sternal marrow of an adult by this method over a ten-day period.

Complications

The possibility that gangrene of a toe or finger will result from a nerve block with procaine-

epinephrine solution is emphasized in all standard texts on regional anesthesia. The literature reports two such happenings, one involving a finger and the other a toe.[64, 65]

At some time every surgical team will be called on to face the serious responsibility of a sudden cardiac arrest in the operating room. One such case, which occurred while the patient was receiving an inhalation anesthetic for a left lower lobectomy because of bronchiectasis, is reported in detail by Adams and Hand.[66] The probable cause of cardiac arrest, with treatment instituted that after twenty minutes resulted in a successful outcome, is given.

I was faced with a sudden cardiac arrest in a patient under spinal anesthesia during the last year. Approximately twenty-five minutes after the induction of anesthesia, while the surgeon was carrying out a high abdominal exploration, the pulse and blood pressure suddenly could not be obtained and respiration ceased. Vigorous artificial respiration carried on through an endotracheal tube with oxygen from a gas machine was started immediately, as was cardiac massage through the diaphragm, by the surgeon. One cubic centimeter of epinephrine was injected into the heart muscle, and the arrest was overcome in approximately three to four minutes after the pulse had disappeared. The patient made an uneventful recovery except for the loss of memory for a period of about two days.

Judging from the above experiences and those of Beck,[67] it seems reasonable to make every effort to save the lives of these patients. Prompt, adequate and properly selected methods of stimulating the return of cardiac function and the maintenance of adequate cerebral oxygenation are essential. Artificial respiration must be instituted with a gas machine after an intratracheal tube is inserted. Cardiac massage must be promptly started either through the chest or the left diaphragm. If the operation is not being carried on in the chest or abdomen, a transthoracic approach is quickly made. Small doses of epinephrine — 0.5 to 1.0 cc. — injected into the cardiac muscle seem to be almost a necessity.

The surgical importance of atelectasis is obvious. It may complicate convalescence from any operation, and it is probably the most commonly encountered pulmonary complication after abdominal operation. Schmidt, Mousel and Harrington[68] present an interesting paper dealing with a series of 84 selected cases of postoperative atelectasis. Fifty-eight of the patients were men and 26 were women. The average age of both men and women was fifty years. There were no preoperative roentgenographic signs by which the likelihood of postoperative atelectasis could have been foretold. In 52 of the cases the operations were on the biliary tract or stomach, in 9 cases on the colon, and in 8 cases on the kidney or its surrounding tissues; the number of cases representing other operations probably was not significant. In all cases in which atelectasis followed operation on the kidney, the lung affected was the one corresponding to the side on which the patient was lying. If treatment was begun within forty-eight hours after the complication occurred, the results were excellent. If the complication existed for seventy-two hours or longer before treatment was begun, recovery was usually slower, since secondary pneumonia had usually developed.

Military Anesthesia

In an excellent article that brings the history of anesthesia in war surgery up to date since ether was discovered in 1842, Pender and Lundy[69] concluded with these predictions about anesthesia in the present war:

> Chloroform will be the reserve anesthetic agent for use under adverse circumstances.
>
> Ether will form the foundation anesthetic agent when other agents are not satisfactory.
>
> Local anesthesia will be either used alone or supplemented whenever possible.
>
> Nitrous oxide and oxygen will be most useful for simple induction and for short operations.
>
> Spinal anesthesia administered by experienced hands will be safer than ever before for operations performed below the diaphragm.
>
> Quick-acting barbiturates administered intravenously will be used more often than any other type of anesthetic agent.
>
> Rectal anesthesia will be used seldom.
>
> Cyclopropane will be unequaled for anesthetizing many patients in base hospitals.
>
> The intratracheal method will be almost the routine manner of administration of the volatile anesthetic agent.

Martin[70] believes that the advances in anesthesiology since World War I are reflected in its inclusion in the organization of hospitals of the United States Army.[71] Anesthesiology, for the first time, was set aside as a section by itself on the Surgical Service of the Tilton General Hospital, Fort Dix, New Jersey, for instruction of medical officers in the fundamental principles of anesthesiology.[72]

Several anesthetists have related their experiences in England[73] and the Middle East[74] at large general hospitals. Much of the work was of the same general character as that seen in any large civilian hospital, except for the emphasis on traumatic cases. Inhalation anesthesia by the intratracheal route seems to have been most popular. Intravenous Pentothal Sodium was used widely for minor surgery, spinal anesthesia was seldom

used, and local anesthesia was used little if at all.

Because the problems of anesthesia in a small portable hospital immediately behind the front lines are so entirely different from those encountered at a base hospital, inclusion in this article of part of a recent communication seems timely. Swinton,[75] commanding officer of a small portable hospital that functioned for months in New Guinea, writes as follows about anesthesia:

> In about 500 operations that I saw performed practically in the front lines, Pentothal Sodium was used almost routinely. These boys come in tired out, dirty and already heavily narcotized at the aid stations. All of them are frightened, and most of them are in more or less shock. We use plasma by the gallon. Pentothal served 95 per cent of all purposes. Spinal anesthesia can be used in a few of the abdominal cases if the shock can be quickly and safely controlled, but I stuck to ether in these cases. It is hard work, though, when one is spoiled by the relaxation of spinal anesthesia. Pentothal is easy to carry, easy to prepare, not bulky, and almost foolproof in any operation requiring up to forty-five minutes to one hour. Most front-line surgery can be done very rapidly and in less time than in civilian practice. No aftereffects and quick recovery so that evacuation is not interfered with are important points in this work. One patient in this group died, and Pentothal should never have been given to him — just plain stupid selection of an anesthetic agent.

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Vol. 19

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 29311

PRESENTATION OF CASE

First admission. A fifty-two-year-old meat dealer entered the hospital because of abdominal distress and jaundice.

He was well until three weeks before admission when he developed attacks of severe abdominal and substernal distress after eating that lasted for several hours and were often associated with anorexia. At the same time a steady aching discomfort developed between the shoulder blades and persisted to the time of admission. During one attack of distress he vomited bile-stained food without much relief. Nausea and anorexia developed and he became constipated. Four days prior to admission a physician told him that he was jaundiced and prescribed a bland fat-free diet, which relieved the epigastric distress and anorexia. The jaundice, however, deepened, the urine became dark, and the stools clay colored. There were no chills or fever. The patient denied the use of alcohol or drugs. During his illness he was said to have lost a great deal of weight.

The family and past histories were noncontributory.

Physical examination disclosed a well-developed, moderately jaundiced man in no apparent discomfort. The scleras were deeply jaundiced. The heart and lungs were normal. There was a sense of fullness in the right upper quadrant of the abdomen but no masses were felt, and no tenderness or rigidity was elicited.

The blood pressure was 120 systolic, 70 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood revealed a hemoglobin of 12.8 gm. and a white-cell count of 7800, with 69 per cent neutrophils. The urine showed a + test for bile. A blood Hinton test was negative. The serum protein was 6.8 gm. per 100 cc., the phosphorus 3.3 mg., the phosphatase 17.0 Bodansky units and the bilirubin 3.9 mg. direct and 6.2 mg. indirect. The prothrombin time was 18 seconds (normal, 20 seconds). The stool was greenish brown and repeatedly guaiac negative.

*On leave of absence.

A flat plate of the abdomen revealed a liver that was slightly smaller than normal. The spleen was at the upper limits of normal. No definite stones were seen. On the sixth hospital day an exploratory laparotomy was done, with a preoperative diagnosis of "obstructive jaundice, probably due to a stone in the common duct." At operation the gall bladder was moderately distended. There was no evidence of metastatic disease of the liver. The pancreas was about three times normal size, nodular and irregular. There was no evidence of fat necrosis. The common duct was about twice normal size and no stones were found. A cholecystgastrostomy was done. A pancreatic biopsy was reported as chronic pancreatitis with fibrosis.

Following operation the jaundice cleared, the urine became pale and the stools brown. Between the eleventh and eighteenth postoperative days he was given x-ray treatment (1200 r) over the pancreas. The patient was discharged on the twenty-fourth hospital day.

Second admission (fourteen months later). The patient re-entered the hospital because of the onset of dark urine, clay-colored stools and a nagging, sometimes painful sensation in the back between the shoulder blades. The patient had been fairly well and had been free from jaundice, back pain and malaise until one week prior to entry. Three days prior to entry jaundice appeared. There were no chills, fever, nausea or vomiting.

Physical examination was similar to that of the first admission. The liver edge was palpable two fingerbreadths below the right costal border.

The temperature, pulse and respirations were normal. Examination of the blood revealed a red-cell count of 5,250,000, with a hemoglobin of 15.1 gm., and a white-cell count of 8400, with 57 per cent neutrophils. The urine was normal. The serum bilirubin was 3.4 mg. per 100 cc. direct and 4.35 mg. indirect. The stool was light tan, and guaiac negative. Gastric analysis failed to reveal free hydrochloric acid, either before or after a test meal. The stomach content was guaiac negative.

An x-ray film of the chest was negative.

Because the patient desired to return home to consider operation, he was discharged, unimproved, on the seventh hospital day.

Final admission (six weeks later). After discharge he was awakened several times at night by mild epigastric discomfort that was partly relieved by warm water or milk. Four weeks prior to admission his stools became pale, and the urine dark brown. Three weeks prior to admission the jaundice deepened and generalized pruritus developed. His appetite decreased, but he had no nausea, vomiting, hematemesis or melena. Two

weeks prior to admission he developed diarrhea and often had two to seven movements a day for three or four days, but this was relieved by tincture of belladonna. The liver was felt 2 cm. below the costal margin in the right anterior axillary line, 6.5 cm. below in the midclavicular line, 8 cm. below the xiphoid, and 6 cm. below the left costal margin. The spleen was neither palpable nor percussable. There was no shifting dullness or fluid wave.

The temperature, pulse and respirations were normal.

The urine showed a + test for albumin, a ++++ test for bile and no urobilinogen. The serum bilirubin was 10.4 mg. per 100 cc. direct and 14.8 mg. indirect. Five days later it was 12.3 mg. direct and 17.5 mg. indirect. The prothrombin time was 23 seconds (normal, 18 seconds). The stool was gray, guaiac negative and contained neutral fat.

The jaundice increased, and the patient complained of increased urinary frequency and vague abdominal discomfort. After preparation with saline-glucose infusions and water-soluble vitamin K, an exploratory laparotomy was performed on the eleventh hospital day.

Differential Diagnosis

Dr. Robert R. Linton: The history of the first admission without any question indicates that we are dealing with a patient with obstructive jaundice. There are a number of conditions that can produce obstructive jaundice, the commonest of which, of course, is cholelithiasis with a stone in the common duct or an extrahepatic lesion producing pressure on the common duct, such as carcinoma of the head of the pancreas or carcinoma of the papilla of Vater. Carcinoma of the biliary passages can also produce obstructive jaundice, but it is my opinion that this lesion produces obstructive jaundice of complete degree and of a much more rapid nature than this man developed. Another cause of jaundice that one ought to consider is cirrhosis of the liver. This is usually not complete obstruction, however, and associated with it, one usually finds a large spleen. We have evidence here by x-ray and physical examination that the spleen was relatively small or normal in size. Another condition that one encounters is pancreatitis, which sometimes produces a sclerosing type of lesion that obstructs the common duct as it passes behind the duodenum.

I do not believe there is anything in the laboratory findings of diagnostic importance. It is interesting that the phosphatase was elevated, which is the usual finding in obstructive jaundice. The bilirubin was elevated but not markedly, 3.9 mg. per 100 cc. direct, with a total of 6.2 mg., which indicates that the patient had obstructive jaundice rather than jaundice due to blood destruction. The prothrombin time was essentially normal, so that he did not have a hemorrhagic diathesis.

At the operation we learn that the gall bladder was moderately distended; no stones were found, and the pancreas was enlarged. These observations confirm Courvoisier's law, namely, that a dilated gall bladder in the presence of jaundice usually means extrahepatic biliary obstruction rather than obstruction due to stone. It is of interest that a biopsy of the head of the pancreas was reported "chronic pancreatitis with fibrosis." Biopsies of the head of the pancreas are, I believe, notoriously inaccurate because of the fact that in carcinoma of the pancreas one may have obstruction of the pancreatic duct with a good deal of thickening and fibrosis of the pancreas, and what one thinks is a malignant lesion is really secondary fibrosis from obstruction of the pancreatic duct by carcinoma. So far as the story at the first admission is concerned one must decide whether one is dealing with carcinoma of the head of the pancreas or pancreatitis due to unknown causes, both of which produce obstructive jaundice. The fact that the patient received 1200 r of x-ray therapy makes me inclined to think that at that time the diagnosis of cancer of the pancreas was favored over that of pancreatitis.

At the second admission, fourteen months later, the patient re-entered because of the onset of dark urine, clay-colored stools and a painful sensation between the shoulder blades. He had been relieved temporarily by the cholecystgastrostomy, which apparently functioned very well for a little over a year, when his symptoms began to return.

After a period of six weeks from the time of the second admission the patient returned with evidence of marked obstructive jaundice, which had resulted in a large liver. It is interesting that he developed diarrhea of from two to seven movements a day for three or four days. If he had pancreatic obstruction, I am surprised that that came on so late. If he had had pancreatic-duct obstruction without any external pancreatic secretion going into the intestinal tract, I should have thought that he would have had steatorrhea earlier. His condition was getting worse, as indicated by the serum bilirubin, which jumped from a total of 14.8 to 17.5 mg. in five days' observation. I believe the diagnosis still lies between cancer of the head of the pancreas and chronic pancreatitis.

In favor of its being carcinoma of the head of the pancreas is the fact that this is the commonest

lesion that produces obstructive jaundice in cases in which the pancreas is involved. I have seen one patient who had had cholecystgastrostomy who lived for three years before he finally died of carcinoma of the pancreas; we wondered, until we finally did ascertain what his trouble was at autopsy, whether we were not dealing with chronic pancreatitis. The case we are discussing did not go quite that long, only fourteen months. Another interesting point is, Why did this man do so well for over a year and then develop obstructive jaundice? Certainly the cholecystgastrostomy worked well at first, and why it did not continue to work well seems a little strange. The fact that it did not work continuously and relieve the jaundice permanently suggests that one was dealing with a malignant lesion and that the malignant disease had eventually involved the cholecystgastrostomy. We have no evidence, however, so far as physical examination goes, that the patient had metastatic disease involving the abdominal cavity, such as a nodular liver or other masses.

On the other hand if one assumes this is pancreatitis, then one has to postulate that for some reason or other the cholecystgastrostomy failed to function after a period of time. I think we have observed on occasions that cholecystgastrostomies and choledochoenterostomies do close off spontaneously if the normal biliary circulation through the ampulla of Vater is re-established, and I think that is a possibility in this case. If so, it would favor the diagnosis of pancreatitis. It seems to me on the evidence presented here, however, that the more likely diagnosis is carcinoma of the pancreas with extension and finally obstruction of the short-circuiting operation that was performed.

DR. BENJAMIN CASTLEMAN: Dr. Allen, will you tell us your impression of the case?

DR. ARTHUR W. ALLEN: Dr. Jones and Dr. Benedict are both interested in this patient. Dr. Linton's reasoning about the first admission was I think in accordance with our own. We thought it was possible that, with the biopsy of the pancreas, we did not obtain a piece of the true lesion, although Dr. Mallory made sections of it and felt quite certain that it was an inflammatory process. Dr. Jones has just reminded me that the process involved the entire pancreas and was not localized to the head, as we nearly always see it in cases of carcinoma of the pancreas with jaundice.

Dr. Linton wondered why the patient had radiation afterward and thought that might help him in his diagnosis of malignant disease. The reason he had that treatment was based on the idea of Morton,* of Rochester, New York, who has suggested that, since the pancreas is so much like the parotid gland in its structure and since radiation works so well in acute parotitis, mild radiation in pancreatitis may be of value. So we gave a small amount of x-ray therapy, 1200 r, divided in four doses. He recovered so completely that we believed that he really did have an inflammatory rather than a malignant lesion. Dr. Jones and I even considered the possibility of disconnecting the cholecystgastrostomy for fear of an ascending cholangitis. When the patient came in to Dr. Jones for a check-up six months later, he found evidence of a good deal of liver damage, which he will tell you about, and the question of reoperation was dropped, until he became jaundiced again and began to have symptoms. We reasoned very much as Dr. Linton did; that is, we might have made a mistake in our original diagnosis and the patient might have had a respite from carcinoma during this period. Dr. Benedict therefore performed a peritoneoscopy and found a swollen liver without any nodules; a biopsy showed obstructive jaundice.

We then explored the patient, after adequate preparation. He had 100 per cent dye retention in the liver. At operation, we found a small, hard pancreas, which was possibly one fourth the size that it was originally, and another biopsy specimen, a generous one, examined by Dr. Castleman showed fibrosis of all the pancreatic elements with nothing but islet cells left in the gland. We therefore reasoned that he had had inflammatory disease from the start and that the reason the cholecystgastrostomy had closed was exactly as Dr. Linton suggested — during a period of his early convalescence the portion of the duct that went through the pancreas was released, the duct functioned again and therefore nature had closed the artificial opening. We further reasoned that, at this time, a permanent arrangement for the passage of bile into the intestine should be made. We therefore anastomosed the cut end of the jejunum to the fundus of the gall bladder in an isoperistaltic direction, re-anastomosing the other end of the jejunum to the side of the gut after the method of Roux. The procedure was well planned and there were no difficulties, but, as Dr. Castleman will tell you, it was too much for a man who was as sick as this one. The patient died two days later with what we believed to be liver failure, quite like the kind of death we used to see in patients who had their hepatic arteries tied accidentally.

*Morton, J. J., and Widger, S. Diagnosis and treatment of acute pancreatitis. *Ann. Surg.* 111:851-863, 1940.

DR. CHESTER M. JONES: There are one or two other points of interest. I saw this patient a year after the first operation and followed him closely. He had no symptoms except diarrhea. He recovered from his jaundice, about a month after the first operation there being no trace of it. At that time the liver was two fingerbreadths below the costal margin. In other words it had diminished in size appreciably. Six months after operation he was feeling better and had no jaundice, the liver was just barely palpable, the bilirubin was 0.4 mg. per 100 cc., a perfectly normal figure, and the dye retention was 10 per cent. That made me wonder whether he had some permanent liver damage.

Six months later he had no jaundice, but the liver was two fingerbreadths below the costal margin, definitely larger. Because of the discrepancy we checked the laboratory findings and found that he had 60-per-cent dye retention and increased blood bilirubin. He remained free of jaundice until three or four weeks before he finally was operated on, and then, rather suddenly, clinical jaundice recurred. At that time the dye retention was 100 per cent. Dr. Allen and I thought that regardless of the cause of the block there must have been a lot of liver damage, which was explainable on the basis either of diffuse hepatic involvement by carcinoma, which was unlikely, or a diffuse process in the nature of a biliary cirrhosis. The biopsy specimen that Dr. Benedict took had the microscopic appearance of biliary cirrhosis. In other words, the biopsy fitted the clinical picture, but it was still impossible to tell what was the underlying cause.

DR. LINTON: I still do not see why the patient became jaundiced so suddenly at the end.

DR. JONES: I think what happened was that he had a fairly active low-grade inflammatory process involving the pancreas and probably the liver itself. At any rate at a point in the course of the illness the cholecystgastrostomy closed over completely. When Dr. Allen operated he could not get a probe into the opening of the gastrostomy. Is that not correct, Dr. Allen?

DR. ALLEN: Yes; there was no opening into the stomach.

CLINICAL DIAGNOSIS

Obstructive jaundice.

DR. LINTON'S DIAGNOSIS

Carcinoma of the pancreas?
Chronic pancreatitis?

ANATOMICAL DIAGNOSES

Chronic pancreatitis, severe, with stenosis of common bile duct.
Obstructive biliary cirrhosis of liver.
Cholelithiasis.
Choledocholithiasis.
Ascites.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The biopsy showed that the pancreas was, as had been described at the second operation, very small and fibrotic. The sections from the autopsy material confirmed the biopsy sections, showing a diffuse interacinar and perhaps interlobular type of chronic fibrous pancreatitis. There was atrophy of the acinar cells and replacement of much of the parenchyma by fibrosis and lymphocytic infiltration so that only the islet cells and ducts remained. This was much severer in the region of the head of the pancreas but was also present throughout the organ. The opening of the bile duct at the ampulla was tiny, and the common bile duct above was markedly dilated, about 3 cm. in circumference. This stenosis had undoubtedly been produced by the surrounding fibrous pancreatitis. There was no carcinoma. In the common duct, as well as in the gall bladder, we found muddy material and a few small stones (0.5 to 1 mm. in diameter), which was evidence that the infection was still going on in the biliary tract.

The liver showed widespread fibrosis of the biliary type, with proliferation of the bile ducts characteristic of fairly long-standing obstructive jaundice. There were 2 liters of bile-stained fluid in the abdominal cavity. The anastomoses were intact, and I believe that death was due to liver failure. I find it hard to conceive that the bile duct was ever patent enough to allow for a closure of the anastomosis because of disuse. I think he was getting all his bile through the anastomosis until it closed. Why, I do not know.

DR. ALLEN: My reasoning about it is that at the time of the first operation the pancreas was tremendously swollen, four times the normal size, from the inflammatory process, that the edema around the pancreatic portion of the duct produced the jaundice and then when the anastomosis was established the inflammation in the pancreas receded enough afterward to allow a temporary passageway for the bile to go through its natural course. During the temporary normal passageway, the anastomosis shut down. The duct did not completely close off — again due to the fibrosis — until one of these 1-mm. stones got down into

the narrow channel. That probably explains the question Dr. Linton asked about the suddenness of the final jaundice. As a matter of fact it took two or three weeks for it to become complete.

DR. CASTLEMAN: I do not believe that the bile duct would open when the pancreas became scarred; in fact this might tend to close it more completely.

DR. ALLEN: We have had many cases of jaundice associated with pancreatitis that have completely cleared up. I have seen only one previous case of complete fibrosis of the pancreatic portion of the bile duct. It may happen quite frequently, but that is the only other one I have seen. In that patient the pancreatitis was secondary to a penetrating duodenal ulcer.

DR. CASTLEMAN: This is the first true case of widespread chronic pancreatitis that I have ever seen. Mild degrees of focal chronic pancreatitis are not uncommon autopsy findings, but this severe form is distinctly unusual.

DR. LINTON: The original obstruction could have been due to edema. Fibrosis would take months.

DR. ALLEN: Yes; "edema" is the word for the early episode, and "fibrosis" for the final one.

DR. JONES: Furthermore, the patient had a slight amount of bile going through until the day of operation. X-ray films taken three weeks before failed to show barium going into the gall bladder, which it will do if the stoma is patent.

DR. ALLEN: That is correct. At the second admission roentgenograms showed no passage of barium from the stomach to the gall bladder.

DR. JONES: Dr. Allen and I discussed this case after operation. If we were confronted with a situation like this, where the liver was badly damaged, it would be worth considering a two-stage operation, simply relieving the block for the moment with drainage and doing the complete operation later. This is all in retrospect, but I think it should be mentioned.

DR. ALLEN: I have disliked doing two-stage operations for this type of obstructive jaundice because we rarely succeed in getting to the second stage. Sudden decompression of the liver has caused the patient to continue his decline. Possibly we should have been smart enough to have thought of operation when the dye retention rose to 60 per cent. We may never see another patient like this. It is an unusual case.

DR. LINTON: I wonder why you did not do the Roux type of operation rather than cholecystgastrostomy at the first operation.

DR. ALLEN: I expected this to be a temporary affair, and planned to disconnect it after the patient had recovered from the pancreatitis. I did not suppose he would develop fibrosis.

CASE 29312

PRESENTATION OF CASE

First admission. A seventy-nine-year-old Italian laborer entered the hospital because of a chronic ulcer of the right elbow occurring in the scar of an old burn.

Approximately forty years prior to admission the patient burned both elbows severely. These healed slowly with a great deal of scarring but without limitation of joint motion. Approximately one year prior to admission the scar about the right elbow ulcerated, often bled a great deal and never completely healed despite local treatment.

The family and past histories were noncontributory.

Physical examination disclosed a fairly well-preserved old man who seemed apprehensive. The heart, lungs and abdomen were normal. On the dorsal aspect of the left elbow over an area approximately 5 by 4 cm., involving the lower end of the upper arm and an equal area of the lower arm, were irregular scars traversed with many firm crusted ridges. The involved area of the right elbow measured approximately 14 by 12 cm. and was almost symmetrical in position to that of the left arm. In the center was a shallow ulcer, 12 by 8 cm., covered by shreds of necrotic tissue, fresh blood and greenish-yellow purulent exudate. There was almost no granulation tissue.

The blood pressure was 148 systolic, 90 diastolic. The temperature, pulse and respirations were normal.

Examination of the blood revealed a red-cell count of 4,440,000, with a hemoglobin of 84 per cent, and a white-cell count of 8200. The urine was normal. A blood Hinton test was negative.

X-ray films of the right elbow showed a large area of bone destruction from the upper one third of the shaft of the ulna with some soft-tissue swelling. There was no evidence of new-bone formation. There was a pathologic fracture through the area of destruction. A chest roentgenogram showed clear lung fields. There were several old fractured ribs on the right side. Following a report of epidermoid carcinoma, Grade 2, on a biopsy specimen from the edge of the ulcer of the right elbow, the right arm was amputated at the junction of the middle and lower thirds of the humerus. Dissection of the amputated limb showed extension of the neoplastic tissue from the base of the tumor into the subjacent proximal end of the ulna, with pathologic fracture 4 cm. from the proximal articular surface. Because of the severe local infections, the patient received a preoperative course of sulfadiazine. He was discharged on the eighteenth hospital day.

Final admission (one year later). The patient re-entered because of fever, foul breath and pain in the right chest.

Following discharge the patient was well until four months prior to admission, when he developed a "cold," characterized by cough, fever, chills, sweating and a sharp pain in the left lower chest anteriorly. After three and a half weeks in his community hospital he apparently made a satisfactory recovery, and an x-ray film of the chest prior to discharge was said to have been negative except for "congestion." Three months before entry he had a tooth extracted under local anesthesia.

Approximately six weeks before entry he again developed a cough and complained of a sharp pain across the epigastrium and in the precordial area on coughing. He soon became extremely weak, lost his appetite and went to bed. Three days prior to admission he suddenly coughed up a large amount of bloody, foul-smelling material, and since then he had continued to bring up fairly large quantities of foul-smelling sputum, without blood. During the three days prior to admission he had several chills, with fever as high as 101°F.

Physical examination disclosed an emaciated man with a great deal of respiratory distress. The chest was large, and there was dullness to flatness with diminished breath sounds and coarse moist rales over the posterior right chest below the scapula. In the right axilla a loud "leather-creaking" sound was audible on both inspiration and expiration. There was no diaphragmatic excursion on this side. A blowing systolic murmur was audible over the entire precordium, best heard at the apex. Abdominal examination was negative. The right upper arm stump was well healed, and the scar about the left elbow had not changed since the previous examinations. There was no clubbing of the fingers.

The blood pressure was 115 systolic, 55 diastolic. The temperature was 100°F., and the pulse and respirations were normal.

A chest roentgenogram demonstrated a large abscess above the right diaphragm posteriorly, which was 7.5 cm. across at the fluid level. The abscess wall was rather thick and irregular, and the outlines not sharply defined. No definite tumor mass was seen in the hilar area.

Examination of the blood revealed a red-cell count of 3,800,000, with a hemoglobin of 13 gm., and a white-cell count of 16,000, with 82 per cent neutrophils. The urine was acid and had a specific gravity of 1.020; the sediment contained innumerable red cells, 4 to 6 white cells and several granular casts per high-power field. The sputum was tenacious, foul smelling, and yellow green, with rusty streaks. Bronchoscopy showed no widening, deviation or fixation of the carina. The right upper and middle lobe orifices were normal. The mucosa throughout the right main and lower lobe bronchi was markedly reddened and somewhat edematous and contained a considerable amount of a brownish-red, thin secretion. This appeared to be coming from the lower lobe bronchus, but its exact origin could not be determined. The mucosa was smooth, and there was no intrinsic mass or evidence of extrinsic pressure.

The patient continued to run a fever ranging between 100 and 102°F. Postural drainage was ineffectual, and on the thirteenth day a first-stage drainage of lung abscess was performed. A chest roentgenogram the next day showed no change in the abscess cavity. In addition there was an area of consolidation in the left mid-lung field. Four days later the second stage was done. The patient died soon after operation.

Differential Diagnosis

Dr. Ralph Adams*: The assumption that chronic irritation was an etiologic factor in the production of this cancer from a burn scar seems to be admissible without argument. The carcinogenic role of continuing low-grade injuries to tissues by infection and by mechanical, thermal and chemical irritants has been well established and is generally accepted. Taylor, Nathanson and Shaw[1] reviewed 430 cases of carcinoma of the extremities and found definite precancerous lesions to exist in 196 cases. Eleven cancers occurred in the sinuses of chronic osteomyelitis, 13 in varicose ulcers, and 23 in the scars of old burns. The 11 cases of cancer found in osteomyelitis sinuses all had appeared in lesions more than fifteen years old. I know of no case in which cancer has appeared in a chronic varicose ulcer in a shorter period. There is in the literature no report of carcinoma appearing primarily in an empyema sinus, but I have one unpublished case in which epidermoid carcinoma developed in a chronic empyema sinus twenty-six years after its onset. However, highly malignant cancer has been observed in scars of old burns within two years. The point being made is that an ulcer appearing in an old burn scar more than fifteen years after the original injury is almost surely malignant and should be treated as such immediately.

This hospital had no opportunity to offer treatment until the cancer had advanced to bone destruction and carried out the appropriate therapy — amputation. Metastatic disease in the chest, the commonest site of carcinomatous metastases

*Surgeon, Lahey Clinic.

from the upper extremity, was properly excluded so far as possible by negative chest roentgenograms preoperatively.

Within eight months, however, the patient developed signs of lung and pleural involvement and received clinical relief of symptoms by rest in his local hospital; however, x-ray signs of "congestion" persisted, indicating that he had more serious disease than a "cold" or congestion or simple bronchopneumonia. A week after leaving the local hospital and three months before coming here he had a tooth extraction under local anesthesia. Six weeks thereafter and six weeks before entry here, he again developed signs of pneumonitis with infection, and three days before entry a diagnosis of putrid lung abscess was made, which was self-evident when he coughed up foul, bloody pus.

The record is not clear on this detail but I dare say that the patient was never entirely free from cough and a sensation of something wrong in his chest from the original chest episode four months prior to entry until his eventual admission, for the following reasons. In the first place, six weeks is an unusually long interim between a tooth extraction and the appearance of a lung abscess if such is developing. An additional five weeks, for a total of eleven, is in my experience unique between the onset of suppurative pneumonitis and the production of foul sputum. Secondly, according to statistics, a patient with this diagnostic and symptomatic background should have malignant disease in his chest. Thirdly, although the record does not mention it, the first chest x-ray film at the time of the second admission shows distinct erosion of the left fifth rib and adjacent translucence in the peripheral lung field, as well as the described abscess in the opposite lung. Fourthly, the walls of the abscess are much denser and thicker and more irregular than one is accustomed to see in putrid lung abscess but are characteristic of abscess secondary to malignant degeneration. And, finally, — and I shall ask the X-ray Department for confirmation or rebuttal in a moment, — it is my impression that the chest x-ray film taken one day after the first-stage drainage of the right lung abscess, and twelve days after the previous film, reveals marked destruction of the left fifth rib and pathologic fracture in addition to the area of consolidation in the left mid-lung field cited by the case abstract as having just appeared. A few years ago the statement was frequently made that metastatic pulmonary lesions do not cause hemoptysis, but since then a few exceptions have been encountered,[2] and we have to abandon the rule as a statement of invariable fact; it is, however, a good generalization. Similarly, I have one proved example that metastatic malignancy can suppurate to produce bloody and foul sputum, and I believe that this case furnishes a second example. The bronchoscopic findings are consistent with that theory. The point whether the abscess is pyogenic or cancerous is an academic one, but it is a feature of the case that requires discussion.

Before making a final diagnosis may I have a first-hand interpretation of the films from the X-ray Department?

Dr. Benjamin Castleman: The following statement appears in the x-ray report, "The posterior portion of the left fifth rib cannot be traced as it crosses the area of involvement. I believe the patient should have a film of the rib." Apparently that film was never taken.

Dr. Milford Schulz: It is quite obvious that the posterior portion of the left fifth rib is involved. Certainly the short interval of time suggests that the rib must have been involved in the earlier film. Yes, it is; here is an area of destruction in the same place — apparently a fracture occurred in the meantime.

Dr. Adams: In my halting clinical way I hesitated to arrive at a diagnosis of the rib lesion and took the liberty to ask Dr. Hugh Hare, a radiologist, to check that finding, which he did.

In conclusion, I shall state my diagnosis as carcinoma in an old burn scar of the right arm, with chest-wall and pulmonary metastases and putrid lung abscess.

Dr. Helen Pittman: When I saw this man, — I acknowledge that I missed the lesion in the rib, — he obviously had a stinking lung abscess. I cast my vote in favor of its being distal to an intrabronchial metastasis, going on the same reasoning as Dr. Adams has used.

Clinical Diagnoses

Lung abscess, right lower lobe.
Carcinoma of lung (? primary or metastatic), right lower lobe (?).
(Carcinoma of right arm.)
Amputation of right arm.

Dr. Adams's Diagnoses

(Epidermoid carcinoma, in scar of burn of right arm.)
Metastatic epidermoid carcinoma of lungs, with secondary suppuration, and of ribs.

Anatomical Diagnoses

(Epidermoid carcinoma in scar of burn of right arm.)
Metastatic epidermoid carcinoma of lung, right lower lobe, with secondary suppuration.

Metastatic epidermoid carcinoma of ribs and liver.
Pulmonary abscesses, left upper lobe.
Empyema, bilateral.

Pathological Discussion

Dr. Castleman: The second-stage drainage of the large abscess was done, and at that time a biopsy of the wall of the abscess was made. The diagnosis was epidermoid carcinoma. The patient died the day following the drainage.

At autopsy there was empyema on both sides. The abscess had been unroofed and was lined with shaggy gray-green granular tissue. Although grossly it looked like an ordinary lung abscess, epidermoid carcinoma was found in its wall microscopically. In other words, all but a rim of tumor had become necrotic. This was not an abscess distal to a tumor but one within the tumor. In the left upper lobe there were two abscesses that in gross looked very much like the one in the right lower lobe, but sections of both these abscesses showed no evidence of carcinoma. They appear to have been secondary lung abscesses, probably from the infected tumor. Unfortunately no section of the rib was made, but there is no doubt that it would have proved to be metastatic epidermoid carcinoma. A section of the liver also showed metastatic tumor.

When I first saw the biopsy specimen of the right lower lobe I was doubtful whether it was a primary carcinoma of the lung or a metastasis from the carcinoma of the arm. The former is still a possibility, but the peripheral location of the lesion and the similarity of the histologic appearance of the two cancers make metastatic carcinoma more likely. The bone and liver metastases could come from either primary tumor.

Dr. Fletcher H. Colby: Did you find the source of the blood in the urine?

Dr. Castleman: No. There were a few changes in the tubules that suggested degeneration, perhaps due to drug therapy, but I hesitate to say much about it because the autopsy was done sixteen hours after death, when one usually finds post-mortem tubular degeneration.

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PROCUREMENT AND ASSIGNMENT OF NURSES

Last week the War Manpower Commission announced that its subdivision in charge of nurse procurement and assignment, the Nursing Supply and Distribution Unit, had been made an integral part of the Procurement and Assignment Service. The Nursing Division will be supervised by the Directing Board, of which Dr. Frank H. Lahey is chairman, and as with the divisions covering physicians, dentists, sanitary engineers and veterinarians, the latter is charged not only with recruitment of sufficient nurses to meet the needs of the armed forces but also with minimum adequate nursing care for nonmilitary governmental agencies, the civilian population and industry.

Two nurses, Miss Katherine Tucker, of Philadelphia, and Miss Laura Grant, of New Haven, Connecticut, have been appointed to the Directing Board, and the latter will be assisted by the Nursing Advisory Committee, in addition to newly appointed representatives on the already existing advisory committees that are concerned with problems affecting nurses. The work at the Washington office will be under the direction of Miss L. Louise Baker, an assistant executive officer of the Procurement and Assignment Service, assisted by Miss Ruth A. Heintzelman.

The field activities of the Nursing Division will be carried out by state and local committees. At the former level, the Supply and Distribution Committee of the Nursing Council for War Service, which represents the various nursing organizations in each state, will act as the State Committee for Nurses of the Procurement and Assignment Service; whereas local matters will be handled by the nursing councils in each community. Both the state and the local committees will function independently of but in co-operation with the corresponding committees having to do with the procurement and assignment of physicians.

Because of all this it seems likely that many of the present-day problems dealing with nurses will be handled more expeditiously and more efficiently than they have been in the past.

ARNOLD CARL KLEBS*

The death of Arnold Carl Klebs, a distinguished American physician, in Nyon, Switzerland, on March 6, 1943, brings to a close a life of unusual achievement in medicine and medical bibliography. Known to comparatively few physicians of the present generation in America, his influence, nevertheless, was widespread among a small group of doctors particularly interested in medical history.

*An exhibit of books, pamphlets and pictures having to do with Dr. Klebs is now on display in the rotunda of the Boston Medical Library.

As a specialist, moreover, he was a leading figure in this country at the turn of the century in the fight against the "great white plague." In later years his work as the bibliographer of the scientific and medical incunabula was deeply appreciated in scholarly circles. Klebs, like his predecessor, Conrad Gesner, kept his home open in Switzerland to a host of American visitors who found his delightful villa at Nyon, on the shore of Lake Geneva, a welcome resting place in their peregrinations about Europe. Many a weary doctor, exhausted from a great international congress, sought relaxation in this quiet retreat. One found, moreover, an energetic and active man ready to exchange ideas in a stimulating and brilliant manner, often prodding his friends to bring out the best that was in them, and at the same time adding to the conversation, based on a wealth of experience, a keen summary from his own mind. Klebs was, moreover, an ardent correspondent with physicians both in Europe and America. In modern times he must have had few equals, and his pungent, philosophic letters are now the treasured possessions of many who kept this literary and scientific bond throughout the passing years.

Son of Edwin Klebs,[1] an early student of pathology and the co-discoverer with Loeffler of the diphtheria bacillus, Klebs was born in Berne, Switzerland, on March 17, 1870. His early years were peripatetic for, before he received his medical degree at Basel in 1895, his father had held successive chairs in the universities at Berne, Würzburg, Prague, Zurich and Carlsruhe. Klebs became well grounded in the classics and spoke and read with equal facility German, French, Italian and English. One can hardly conceive of a training wider in scope, and as the years went by, he always stood out as an internationalist of the first degree. Because of his facility in languages, he could easily and quickly grasp facts and ideas difficult for many because of language deficiencies. His keen mind, moreover, seemed to miss little.

After receiving his medical degree[2] in 1895, Klebs served as an instructor in pathology in Zurich, spent a summer as locum tenens at Vitznau and carried on some postgraduate studies at London and Paris. It was this thoroughly trained and brilliant student who came to America with his father in 1895. The elder Klebs first settled in Asheville, North Carolina, where he conducted laboratory and clinical investigation in a private tuberculosis sanatorium. Within a year, however, he was called to the chair of pathology at Rush Medical College in Chicago, a position that he held until 1900, when he returned to Europe. Before he left, his son, who in 1898 married Margaret Forbes, daughter of J. Malcolm Forbes, of Milton, Massachusetts, went to Chicago to practice, after having acted as head of a tuberculosis sanatorium in Citronelle, Alabama. He became a citizen of the United States in 1904 and remained in Chicago until 1909. During this period his main interests were in tuberculosis, and he soon became a recognized leader in the field. As director of the Chicago Tuberculosis Institute he was an ardent advocate of the open-air treatment, then an innovation, and he energetically supported the early work of Trudeau and others. Klebs's forceful personality was soon recognized by Billings, Musser, Jacobs, Osler and other students of tuberculosis throughout America. He worked hard, reading papers in various parts of the country, and finally culminated his endeavors in the editorship of a volume by American authors entitled *Tuberculosis*,[3] published in 1909. As a background for this book he collected over three thousands reprints of articles on tuberculosis. These he carefully analyzed and published as a bibliography appended to the work. For authors he sought the best in the field, and contributions were forthcoming from Baldwin, Brown and Trudeau, of Saranac, Biggs, of New York, Coleman, of Augusta, Georgia, Minor, of Asheville, North Carolina, and Webb, of Colorado Springs. Unusually clear Roentgen plates for the time were furnished by Cole, of New York.

This volume was the best summary in English of the subject in 1909 and still may be read with profit. Klebs kept his interest in tuberculosis after 1909, although he did not take an active part in the campaign against it except on rare occasions. At the Fifteenth International Congress on Hygiene and Demography, held at Washington in September, 1912, he served as vice-president of the Section on the Control of Infectious Diseases.

Before his retirement in 1909, Klebs had married for a second time, his first wife having died in 1899. He went to Switzerland to live, first at Ouchy-Lausanne, and later at Nyon. Although making his home abroad, Klebs made frequent visits to the United States, and indeed lived in Washington during the period of World War I and in New York City subsequently for extended periods. Although he never forgot his adopted country, his heart was in his native Switzerland, and there at Nyon he established his library, using a small building on the grounds of his villa for this purpose. This two-story structure was literally lined with books and it became a true workshop of an intense, ardent spirit who exhibited, as few others have done, Osler's master word in medicine, "work." In this building, so delightfully situated, he deposited his father's books on pathology and allied subjects and assembled the apparatus necessary for his historical research.† Whatever he did, he did thoroughly, and each paper that came from his pen in later years was the result of many hours and even years of carefully planned research.

Klebs first historical investigation concerned variolation, stemming from his father's interest in the subject. To his review of the subject,[4] read before the Johns Hopkins Hospital Historical Club in 1912, he characteristically added a bibliography of six hundred items, and followed this with a paper in German on the same topic in 1914. This work brought him in contact with early American medicine: Zabdiel Boylston, Cotton Mather, New England and the Indians, subjects which continued to interest him throughout his life.

His next major work related to Leonardo da Vinci. He read a paper on da Vinci's anatomical studies[5] before the Society of Medical History of Chicago in 1915, at the same time, no doubt, renewing his old friendships in that city. He was living in Washington at the time, working in the Army Medical Library, and had already started his studies on incunabula, using the collection in that library as the basis for his fundamental researches in this field. He began by cataloguing those at hand, and soon contributed some sound ideas regarding classification of incunabula in general.[6] Klebs's scheme was widely adopted by librarians and cleared up many points in descriptive labeling. He was soon led to the fifteenth-century herbals, books scarcely recognized at the time as a distinctive group, and he compiled an extensive catalogue. He[7] later wrote that he had "travelled thousands of miles to visit libraries, to consult numerous catalogues, had an endless correspondence, hundreds of photographs, only to complete and later to correct the data of my list." A similar list of plague tracts[8] was made, followed by more extensive investigations with Sudhoff,[9] published in 1926. These authoritative listings have now become the standard references to the subjects and testify to Klebs's sound scholarship in both their completeness and accuracy.

Various papers on incunabula, appearing from 1926 to 1938, culminated in his classic short-title list of scientific and medical fifteenth-century books,[10] a book constantly referred to by medical bibliographers throughout the world. It was to have been an introduction to a more extensive study, for Klebs had collected photographs and complete descriptions of over three thousand incunabula of medical or scientific interest, and this material lay in his library, ready to be brought to light, at the time of his death. Superbly ordered, it only awaits the final touches of some future scholar. The short-title list, however, is a royal monument to a man whose life was de-

†Dr. Klebs's library will eventually be transferred to the Historical Library of Yale University School of Medicine, where it will be added to the Cushing-Fulton Collection.

voted to sound bibliographic research, and because of it, all scholars are grateful.

Some estimate of the affection and esteem with which Klebs was regarded can be gained from the number of papers published in his honor on his seventieth birthday in 1940. Because of the war most of his European friends were unable to contribute to a birthday volume; however, the Institute for the History of Medicine at Johns Hopkins University issued a large, special number of its bulletin containing papers by his friends and associates.[11] Never a teacher or head of an institute, he had no pupils in the usual sense of the word; but his influence was widespread, and he inspired a group of contemporaries to expand the cultural side of medicine by his writings and by the impact of his forceful personality. In America, his adopted country, he left an enduring stamp on humanistic studies and on the history of medicine.

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MEDICAL EPONYM

Adie Syndrome

This was discussed by William John Adie (1886–1935) in an article entitled "Pseudo-Argyll Robertson Pupils with Absent Tendon Reflexes, a Benign Disorder Simulating Tabes Dorsalis," which appeared in the *British Medical Journal* (1: 928–930, 1931). He writes:

> I wish to draw attention to a benign symptomless disorder characterized by pupils which react on accommodation but not to light, and by absent tendon reflexes.
>
> Five of the six cases I am about to describe came under my notice in the course of a few weeks; the condition therefore cannot be very rare. Though harmless in itself it merits recognition because it is often mistaken for a manifestation of syphilis of the nervous system, with unfortunate consequences for the patients and their families. . . .
>
> . . . . The true Argyll Robertson pupil reacts promptly and fully, often excessively, on convergence, and dilates again as soon as the effort to converge the visual axes is relaxed. In these cases the pupils show the so-called myotonic reactions; they do not respond to light; they contract very slowly through a wide range during a sustained effort to converge; often remain small long after the effort ends, and, when they dilate again, do so slowly.
>
> It seems to me more than probable that some . . . cases with non-luetic Argyll Robertson pupils but normal tendon reflexes are examples of a milder form of the same benign disorder that I have described here.

R. W. B.

OBITUARIES

CLARENCE JOHN BELL

1876–1943

He was the greatest Roman of them all.

It is difficult adequately to evaluate such a versatile personality as Dr. Bell. He typified the highest traditions of the country doctor. His casual mode of dress concealed an alert, well-disciplined mind and character. He had a direct incisive approach to everything he undertook. His medical skill and judgment was of such a character that he held a dominant position throughout his section of the Cape. Not only was he prominent professionally, but as a practical economist his opinion was widely sought. Dr. Bell was a director of the local bank, treasurer of the Methodist Church, a member for many years of the school board and an active supporter of "every good work."

Kindliness, tact and a love of his fellow man were conspicuous qualities that he possessed in full measure. The by-products of his practice, such as the payment of overdue mortgages without thought of personal recompense, and the successful solution of domestic difficulties among his patients, are legion. He possessed a delightful sense of humor, which colored all his dealings.

Wellfleet, to its everlasting credit, appreciating the man and his services, gave a public testimonial dinner in his honor two years ago. All who knew him genuinely mourn the passing of this noble soul.

Besides his wife, he leaves a daughter, Mrs. Stephen Daniel and a son, Richmond.

L. F. J.

MAURICE GERSTEIN

1870–1943

Maurice Gerstein, a practicing physician for forty-five years, died suddenly on July 12, 1943, at Beth Israel Hospital, Boston. Born in Russia on March 1, 1870, he came to this country in 1888 and graduated from New York University Medical College in 1896.

He was a typical successful family doctor who gained the love and esteem of his patients. His records show that during his long practice he was the attending obstetrician in over five thousand deliveries. He was also successful as an organizer, having been a charter member and the first secretary of the medical staff of the former Mount Sinai Hospital, Boston, and a founder of the Greater Boston Bickur Cholin Hospital and the New Century Club. He was an ex-president and supervising censor of the Norfolk District Medical Society and a member of the American Medical Association, the Greater Boston Medical Society and many charitable organizations.

During World War I, he volunteered in the Medical Service Corps, a local medical group, and was appointed chairman of the Soldier's Relief Commission in Ward 16.

Dr. Gerstein was the author of several articles published in various medical journals. He was a founder of the former periodical *The Mount Sinai Monthly* and editor of *The Medical Directory of Greater Boston*, published in 1906.

His sudden death was a shock to his many associates, friends and relatives. He left a landmark in Boston medical and communal life, and died after a full, active and useful life.

S. R. K.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

CONNOR — Thomas J. Connor, M.D., of Arlington, died July 16. He was in his fifty-second year.

Dr. Connor received his degree from the Boston University School of Medicine. He was a member of the Massachusetts Medical Society and the American Medical Association.

CURRAN — Louis F. Curran, M.D., of Dorchester, died July 22. He was in his fifty-eighth year.

Dr. Curran received his degree from Tufts College Medical School in 1917. At the time of his death, he was physician-in-chief of the medical department of the Carney Hospital and clinical professor of medicine at Tufts College Medical School. He was a member of the Massachusetts Medical Society, American Medical Association, American Gastroenterological Association, John Bottomley Medical Society, St. Luke's Medical Guild and the Louis Pasteur Medical Society.

He is survived by his widow, three sons and a sister.

JACKSON — Alton A. Jackson, M.D., of Everett, died July 25. He was in his ninetieth year.

Dr. Jackson received his degree from Harvard Medical School in 1883. He was founder of the Whidden Memorial Hospital and the Everett Visiting Nurses Association. He was a member of the Massachusetts Medical Society and the American Medical Association.

Two sons and a daughter survive.

CORRESPONDENCE

RELOCATION OF PHYSICIANS

To the Editor: The following letter from a physician who has gone into a rural area that was lacking in medical services expresses so clearly and understandingly what has been and is being done throughout the country that I believe it deserves publication.

Frank H. Lahey, *Chairman*
Directing Board
Procurement and Assignment Service
War Manpower Commission
Washington, D. C.

• • •

Dear Dr. Lahey:

It has occurred to me that the following might interest you in connection with your procurement program.

I am sixty-seven years of age, and after specializing in urology for thirty years, came here in November at the request of the Board of Selectmen to take over the practice of the late Dr. Damon.

Wilbraham has a population of 3000 and covers 22 square miles. With the exception of a small Polish group, most of the people are middle-class Americans. The town has no hospital, no drugstore and no district nurse.

Because I was a member of the Massachusetts Medical Society and also came recommended by several well-known medical men in Boston, I was accepted at once by the people, and in two weeks had all I could do.

There are several conclusions that I have arrived at in connection with a medical man past the Government age coming from the city into a country practice. First, it is not necessary or essential for him to make connections with a hospital in a nearby city. The people here wish to be sent to a specialist in Springfield in cases of serious illness, and the medical man has no time even to make a visit on his patient after turning him over to a Springfield consultant. Secondly, I believe that it is impracticable for an older medical man to assume the responsibility of practice in one of these towns unless he has kept up with modern medicine. It is amazing to learn the amount of knowledge the local people have of the newer drugs and newer methods of treatment. An important contributing factor to this is that the public schools have a number of medical examinations throughout the year at which the parents are present. And, finally, it is my opinion that the older medical man need not hesitate to practice in the country owing to fear of nightwork. The people are most considerate and believe that their doctor must be saved as much as possible from overwork. Night calls, except in a rare emergency, can be handled over the telephone, and a call made the following morning. However he must be prepared to see a certain number of people in his office in the evening, since most

of the people are working during the day, and transportation presents difficulties.

The incoming doctor must make up his mind that at least 75 per cent of the work during the winter — November to April — consists of house calls. There are many reasons for this: severe illnesses, fear of contagious diseases on the part of patients, and the ever-increasing transportation problem. The doctor must take his time in his examinations, both in the home and in the office. The visit of the medical man is an event in many of their lives, and it must not be hurried. This is extremely important.

In conclusion, I believe that you, as head of the Procurement and Assignment Service, might help the overworked country medical man by publicizing the idea that the people should notify their medical man in the morning if they expect to see him the same day. I feel very strongly about this and hope that much publicity may be given to it. We country doctors work seven days a week; our meals are always interrupted, and we have little time with our families.

EDMUND L. SAUNDERS

Wilbraham, Massachusetts

NEW PREMARITAL BLOOD-TEST LAW

To the Editor: The following letter was recently forwarded to all physicians licensed to practice in Massachusetts.

VLADO A. GETTING
Commissioner of Public Health

State House
Boston

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Dear Doctor:

A new premarital blood-test law has recently been passed and goes into effect immediately.

The new law (Section 28*A* of Chapter 207 of the General Laws) is essentially the same as the old, except for the following points, which we call to your attention:

(1) Under the new law the examination "shall be made only to ascertain the presence or absence of evidence of syphilis, and shall include a serological test for syphilis."

(2) The law now provides that the health certificate need not be presented until the time of issuance of the marriage license, and the examination and laboratory test must be made not more than thirty days before the date the *marriage license is issued*.

(3) The law now provides that the examination may also be made by "a physician registered or licensed to practice in any other state of the United States."

Until a new supply of forms is available, the old form will be accepted. We suggest that the section number in the next to the last line of the certificate be corrected to read "in accordance with section *twenty-eight* A of chapter two hundred and seven of the General Laws."

VLADO A. GETTING, M.D., Dr.P.H.
Commissioner of Public Health

BOOK REVIEWS

First Aid: Surgical and medical. By Warren H. Cole, M.D., and Charles B. Puestow, M.D., Ph.D. 8°, cloth, 351 pp., with 92 illustrations. New York: D. Appleton-Century Company, Incorporated, 1942. $3.00.

This volume on surgical and medical first aid is one of the most complete that has ever been called to the reviewer's attention. The large number of contributing authors, each an expert in his subject, adds much to the value of the work. All the twenty-one chapters are worthy of most careful reading. Every conceivable question seems to be well covered, and the graphic illustrations are excellent. All the most important advances in the treatment of injuries, such as burns, with accompanying shock, and the correct methods for first aid in the treatment of fractures, are given most careful consideration, with helpful illustrations of transference of the injured with a minimum amount of disturbance and pain.

The first part of Chapter I, entitled "Precautions and Limitations in First-Aid Work," deserves particular attention. Here the question of errors in judgment is taken up. An instance of this is shown in the statement in which the authors truthfully say, "The indiscriminate use of the tourniquet of which first-aid workers are so frequently guilty is often an error in judgment." In the conclusion of this chapter the authors state: "We wish forcefully to remind the first-aid worker of the old proverb which warns us so truthfully that 'a little knowledge is a dangerous thing.' The first-aid worker must know his own limitations in knowledge and ability and abide by them."

This book well deserves a thorough and careful reading by all those who are interested in surgical and medical first aid.

Mental Health in College. By Clements C. Fry, M.D. With the collaboration of Edna G. Rostow. 8°, cloth, 365 pp. New York: The Commonwealth Fund, 1942. $2.00.

The material covered in this book has been gathered in the last ten years by the Department of Psychiatry and Mental Hygiene at Yale University. A mental-hygiene service for students was first inaugurated in 1925 by Dr. Arthur Ruggles, but in the last ten years the work has been carried on by the author of this monograph. The book is a thorough study of mental disease as it appears in college students and is the best study of its type known to the reviewer.

The book is extremely well written, and the problems clearly set forth. There are illustrative case histories. The material was gathered not only from the undergraduate department but also from the postgraduate divisions of the university, where, incidentally, one is surprised to learn that there are so many mental maladjustments. The Commonwealth Fund has made this publication available at a reasonable price, and it is hoped that the book will be widely distributed. It can be recommended without reservation, and should be of use to all educators and to the medical profession in general.

(Notices on page viii)

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